

MONOGRAPHS

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Number 16

Breast Cancer in Younger Women

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Breast Cancer in Younger Women

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Section I: Welcome and Introductory Remarks

Samuel Broder, National Cancer Institute

Welcome to this meeting. The collaborative nature of this meeting is underscored by the participation of Dr. Alexander, Dr. Pinn, and Ms. Amy Langer. This is a time when attention is focused on women's health and breast cancer in particular. It was essential to have a broad forum to consider future research needs. We are very grateful to the National Institute of Child Health and Human Development, the Office of Research on Women's Health, and all the National Cancer Institute (NCI) Divisions for their contributions to planning this meeting. I particularly want to thank Drs. Ted Trimble and Susan Nayfield and the planning committee for their fine work in organizing this conference. I would also like to thank the speakers and moderators who kindly agreed to help us today and tomorrow.

We have many answers about breast cancer in younger women. This conference will help us to both sum up what we know and to design strategies for future research. Some of what we would like to know: Is the incidence of breast cancer in younger women rising? How should we screen younger women? Do younger women respond differently to treatment than older women? Is childbearing safe after a woman has been treated for breast cancer? What about estrogen-replacement therapy? What are the psychosocial implications for breast cancer in younger women?

Just as an aside, I want to remind you to remember and use Physicians Data Query (PDQ). Right now, there are 175 protocols for clinical trials in breast cancer, supported by NCI and others, listed on PDQ. They range from prevention interventions, to drug resistance studies, and to gene therapy. PDQ offers a good way to find out what's being done at NCI Cancer Centers, NCI Cooperative Oncology Groups, and by other National Institutes of Health Institutes.

We welcome your ideas and comments. This is a unique opportunity to make an important difference in the lives of many younger women. I can guarantee you that the deliberations of this meeting will be followed with great interest. I am pleased to announce that the proceedings will be published as a monograph by the *Journal of the National Cancer Institute*. We look forward to your recommendations. Thank you.

Duane F. Alexander, National Institute of Child Health and Human Development

Good morning! I am Duane Alexander, Director of the National Institute of Child Health and Human Development, and on behalf of our Institute and staff, I want to join in welcoming you to this conference and thanking the participants for joining us to share their knowledge and information with us.

Our Institute's interest in this topic relates to that component of our mission that deals with contraceptive and reproductive evaluation; specifically, assessment of the long-term effectiveness and side effects of hormone treatments, such as oral contraception, injectable contraceptives, and hormone-replacement therapies.

We have a long history of involvement in this area. Together with our colleagues in the NCI and the Centers for Disease Control, we have sponsored the Cancer and Steroid Hormone or CASH Study, which has provided us with much of the information that we have about those relationships.

That study, however, dealt largely with older women and largely with older formulations of oral contraceptive pills that had higher doses of estrogens. Today's pills are quite different in having a lower dose of both estrogen and progestin and even having tricyclic pills on the market to be used by a substantial portion of women.

We do not have as good follow-up data on those particular formulations. For that reason, again, with our colleagues in the NCI and the Centers for Disease Control, we have initiated a new study, the NBC Study, or the NICHD Breast Cancer Study, which will be looking at these relationships in younger women.

Over the course of the next 6 years, we will conduct a study of about 10 000 women, half cases, half controls, from age 30 through 64, who will be studied to try and assess the relationships between both hormone-replacement therapy and the newer generation of contraceptive agents and breast cancer, as well as other malignancies.

Dr. Janet Daling, whom you will be hearing from later in the program, chairs the steering committee for this study. This study will also tap into a large minority population by oversampling minorities to try and get at issues of breast cancer in this particular population.

We, our staff and our institute, join with you in anticipating learning from the presentations at this conference and we hope that you not only learn but enjoy being here.

Bernadine Healy, National Institutes of Health; Presented by Vivian W. Pinn, Office of Research on Women's Health

Let me express a "Welcome" to you on behalf of Dr. Bernadine Healy, Director of the National Institutes of Health (NIH), who could not be with us this morning, and on behalf of the Office of Research on Women's Health. Dr. Healy has requested that I convey her remarks to you, and I am pleased to do so.

The young people of our nation are our greatest resource. Their health and well-being must be a primary concern for all of

us. We are here today to discuss a problem that is posing a threat to the health and lives of the young women of this nation. Breast cancer is not just a disease of older women—it strikes the young as well.

We know very little about breast cancer in younger women, but that is changing. The recent focus on women's health issues has raised public and scientific awareness about the need to achieve a greater understanding of this complex disease.

As many of you are aware, the NIH has given top priority to research on women's health and breast cancer, in particular. We have done this because of the tremendous toll breast cancer takes on the health and lives of so many women in this country. Each year more than 180 000 women are diagnosed with breast cancer and 46 000 die from it. Contrary to popular belief, breast cancer does occur in younger women, and experts expect more cases in young women, reflecting the overall increase in breast cancer cases. In fact, today, a woman's chance of developing breast cancer is one in eight; 30 years ago, the chance was one in 20.

Most of what we do know about breast cancer comes from studies conducted in women over 50, the population most likely to develop breast cancer. However, results from postmenopausal studies cannot always be extrapolated to premenopausal women. Pre- and post-menopausal breast cancers present different challenges, which suggest, as some researchers believe, that they may be different diseases. Furthermore, anecdotal reports and limited numbers of young patients in clinical trials have fueled controversy over which treatment choices are the most effective in the younger population.

Breast cancer at a young age can be a devastating disease, emotionally and physically. A young woman with breast cancer may be faced with uncertainties about the long-term effects of chemotherapy and radiation and her future ability to have children. We urgently need the answers to these and other questions if we are to provide hope to the many young women who will develop this disease.

Women of all ages with breast cancer, but particularly younger women, need the most up-to-date, scientifically proven methods of prevention, detection, and treatment in order to have the best opportunity to survive. This meeting represents an important first step toward achieving that goal.

During the next 2 days, your objective will be to define what we know and, even more important, what we don't know about breast cancer in younger women in order to identify those areas that require additional research. Your recommendations will serve as the basis of a comprehensive agenda that will guide researchers in their efforts to fill in existing knowledge gaps. Results, from carefully designed research studies in older women, have led to exciting discoveries that have improved the prognosis and quality of life for thousands of breast cancer patients. Today, we are working to give younger women who have breast cancer the same number of options and the same level of care as older women.

The dramatic increase in breast cancer among women of all ages is one of the most pressing public health threats of our time. Developing a broad-based strategy for research on breast cancer in younger women sends an important message, not only to the research community, but also to the young women of this

country. It serves as a reminder of NIH's commitment to preserving the great resource that America's young women represent. This is an urgent and important mission to fulfill. Your efforts will undoubtedly allow researchers to make significant inroads in improving women's health and lead us closer to the goal of a healthier future for women of all ages.

Dr. Healy and I both thank you for your participation, and we welcome the expertise and wisdom that you will provide during this meeting. Thank you!

Amy S. Langer, National Alliance of Breast Cancer Organizations

Good morning. I am Amy Langer and am very pleased to be here this morning. People in general and those of us in the field think about breast cancer as a disease of older women and, in fact, we know that the median age of onset now is 63. But all around us, and certainly on our telephones at the National Alliance of Breast Cancer Organizations (NABCO), are young women with breast cancer.

NABCO, as a national resource for information about the disease, gets thousands of phone calls from the lay public and from those of us in the field who treat young women. We have actually a pretty large anecdotal data set.

We will hear some statistics, but one NABCO member organization has given us an interesting tracking of cases: the diagnoses at the Marin County General Hospital of invasive breast cancer. In the 1980s, 3% of cases were women under the age of 39, 4% in 1990, 5% in 1991, and 6% in 1992. That is, of course, in the context of increasing incidence of the disease.

Something is going on, a puzzle that we are here to point out and sort out and to discuss the special problems that come with breast cancer in young women, such as the fact that young women don't think they are at risk and neither do their doctors. As a result, they are diagnosed later or diagnosed incorrectly. It seems obvious, but, of course, diagnosis at a young age means a long stretch of life lived in fear, a longer time to worry about recurrence, a larger number of decisions to question and change: where to live, whether to change jobs and risk denial of insurance coverage, whether to bear children, and whether to provide, just in case, for the children already born.

There is also, I think, a problem of tremendous frustration for a generation of women who are predominantly in the work force, handling and processing a lot of information, used to making informed decisions, and finding, with great surprise, how very little is known about breast cancer. So, when they are diagnosed, how very hard it is to feel back in control.

There is the horror of beginning to know contemporaries who have died of breast cancer and realizing, like early in the AIDS epidemic, that the eerie shock of reading the obituary of a 35-year-old is becoming much more commonplace.

Susan Markisz, age 36, is a photographer, and since her diagnosis her work has revolved only around breast cancer—her own breast cancer, her self-portraits with breast cancer, and as a new project, the portraits of other survivors.

Susan was diagnosed in 1988, after finding a lump while she was playing with her kids. She ignored it and then finally had it checked. It was dismissed by a doctor. When it was finally biopsied, it was a 3-cm intraductal carcinoma. She followed recommendations to have a total mastectomy and cyclophosphamide, methotrexate, and fluorouracil chemotherapy.

Her fear, which she lives with every day 5 years later, is that her breast cancer will come back. Her husband (who also has had cancer) and she have individual medical insurance, and she says that their individual policies cost them \$16 000 a year.

Susan took this self-portrait, Fig. 1, and said, "When I made this picture I had just finished 6 months of chemotherapy following a mastectomy for breast cancer in November of 1988. I had lofty ideas and set out to show the world that, hey, look at me, I beat the disease and there is a world full of beauty beyond breast cancer."

"When I printed the photographs, it was like seeing myself for the first time. I didn't see the 'world full of beauty' part, only something very real, which had changed my world, and anger, lots of anger."

Over the last 60 days, I asked the NABCO staff to gather some information on the phone about women who had breast cancer at a young age. I am going to give you profiles of eight of them. In that 60-day period, we got calls from 13 women who had breast cancer at a young age.

Ginger lives in Napa, Calif. She is 42 and she is a single parent. She has a daughter, age seven, and twins who are five. She was diagnosed last year with ductal carcinoma in situ (DCIS), and at the same time, one of the twins was diagnosed with Wilms' tumor. She has had a mastectomy and is seeking opinions about her care because every day she travels 200 miles each way for her twin to be treated.

Ann lives in Boston, Mass. and was 38 at diagnosis. She felt some lumps when she was doing breast self-examination. Her doctor said it was nothing. She had a mammogram and it wasn't "nothing." She had a mastectomy. She rapidly had a recurrence with metastases to the lungs and spine. She is currently filing a suit for misdiagnosis.

Helen lives in Syracuse, N.Y. and she has the exact same story as Ann. She was finally diagnosed at 38. She rapidly had bone metastases. She had several different tumors over 3 years. She says now her biggest problem is money. Her treatment has already cost \$425 000. She fears that her insurance lifetime cap of \$500 000 is approaching and she doesn't know what to do.

Elise lives in New York City and is 41. She is divorced and has two kids. Her mother died of breast cancer. She was so fearful about her own disease that she had a mammogram every 6 months. She was just diagnosed with DCIS. She was told that it was very extensive, that it was a rare type, and that she must have a mastectomy.

Vinnie lives in Escondido, Calif. She was 32 when she was diagnosed. She has two kids, aged seven and four. She discovered her breast cancer herself, a lump, and then denied it for months. By the time she was diagnosed, she was stage IV. She had a double mastectomy. Her mom died of breast cancer, her sister has breast cancer, and her father died of brain cancer.

Frances, aged 35, lives in Nashville, Tenn. She was just diagnosed at stage II. She discovered it herself, doing breast self-examination. Her sister called us. She said that Frances is at the beginning of her journey for information, but she couldn't face calling us herself.

Julie, aged 28, lives in San Francisco, Calif. She is a third-grade teacher and is married with no children. She found her lump in August. It was diagnosed as a cyst and was aspirated. The cytology was negative. It then grew back. Finally, her



Fig. 1. Susan B. Markisz, self-portrait, 1989.

mother insisted on a biopsy in October, after the cyst had doubled in size. It was invasive.

Anita lives in New York City. She found a lump at age 32. She had a needle biopsy and it was suspicious. It was recommended that she have a mastectomy, but she declined. A year later, the lump had grown and she had a lumpectomy. She told us that a new lump has appeared. She called us twice, actually, and most recently she told us she was treating herself with herbs and alternative methods, but she says her lump is now draining through her skin.

We need answers for these women. For those we diagnose early, we need to let them know how to plan their lives and how much hope to have. We need to identify whom to treat aggressively early, with treatments that work. We have to be able to counsel them with more certainty how to live their lives, what joys to embrace, and which to postpone.

I hope that our work today and tomorrow creates easier decisions for young women with breast cancer. Thank you very much!

Section II: Overview

*Joyce O'Shaughnessy**

Good morning and welcome. I am very happy to be here this morning and to be your moderator for this morning's session, during which we will explore the epidemiology, pathology, risk factors, patterns of care, and outcomes of breast cancer in younger women.

Our goal this morning is first to learn as much as possible from the assembled experts about breast cancer in younger women and, second, to determine what it is we know and what questions we need further information about to make progress against this disease. We have an opportunity here today to build a research agenda and to further our understanding of breast cancer in younger women.

As we begin, I would ask each of our speakers and each participant to focus first on what it is we currently know about breast cancer in younger women that distinguishes it from the more classic breast cancer that occurs in women in the sixth, seventh, and eighth decades of life.

Secondly, we need your help today in identifying the high priority questions that need further study in order to unravel the etiology and pathogenesis of this disease.

I think it is fair to say that there exists the perception that breast cancer is becoming more common in premenopausal

women. With the overall incidence of breast cancer rising by 2%-3% per year, it is clear that the absolute number of women who have been diagnosed with breast cancer in the early years of their lives is also steadily rising. From a personal perspective, I very often feel that breast cancer is a disease of young women. The median age of breast cancer patients treated here at the NIH Clinical Center is 46 years, and this has been stable over the past 5 years.

I would like to thank Amy Langer for her emotional presentation; this is indeed a very emotional topic. For those of us who work with young breast cancer patients, the feelings surrounding this issue are just as Amy portrayed. It is perhaps not surprising that younger women, whose breast cancer is often clinically aggressive, are treated in the context of a clinical trial, because investigational studies often take an equally aggressive approach to eradicating the disease.

*Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

Trends in Breast Cancer in Younger Women in Contrast to Older Women

*Benjamin F. Hankey, Barry Miller, Rochelle Curtis, Carol Kosary**

Using data from the Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics, trends in female breast cancer rates were examined for the time period 1973-1989 for the age group 20-39 and contrasted with those for older ages. Only about 7% of breast cancers occur by the age of 40; the risk of developing breast cancer prior to the age of 40 is less than 1%. The incidence trends for women in the 20-39 age group have been essentially stable, whereas for women 40 and older the rates increased steeply during the 1980s (at a faster rate than anticipated based on historical trends) and then leveled off beginning in 1987. Breast cancer mortality has been much more stable over time than incidence. Up to age 40, blacks have a higher incidence than whites. Over age 40, white rates exceed those for blacks, and the absolute and relative differences in incidence increase with advancing age. For whites, 5-year relative survival rates improved with advancing age up to age 50. Blacks under the age of 30 had survival rates similar to whites, whereas, in the older age groups, whites had somewhat better survival rates overall and by stage. The occurrence of second cancers was also analyzed in women with a first invasive breast cancer. Cancers found to occur at higher than expected rates included leukemia and cancers of the breast, ovary, and lung. [Monogr Natl Cancer Inst 16:7-14, 1994]

Summary statistics on breast cancer incidence and mortality, e.g., the age-adjusted rate, are heavily weighted by the higher rates in older age groups. Since breast cancer rates in younger women display patterns that are different from those in older women, it is important to review rates by age group to discern patterns that are hidden by the summary measures.

Data Sources

Data on newly diagnosed cancer cases, including patient follow-up, were collected through the Surveillance, Epidemiology, and End Results (SEER) Program. The SEER Program began in 1973 as part of the National Cancer Program and is administered by the Surveillance Program in the Division of Cancer Prevention and Control at the National Cancer Institute (NCI). The mission of the SEER Program is to provide a basis for assessing progress in reducing the burden of cancer in the general population (1).

The SEER Program currently consists of 11 population-based registries under contract with the NCI to provide data on all cancers diagnosed in residents of their coverage areas. Data collected include cancer site/type, morphology, extent of disease, first course of cancer-directed therapy, and patient follow-up, including cause of death. Data are submitted to the NCI annually. The coverage areas of the 11 registries are the entire states of Hawaii, New Mexico, Iowa, Utah, and Connecticut and the metropolitan areas of San Francisco, Seattle, Detroit, and Atlanta. The county of Los Angeles and the San Jose-Monterey area of California, which is adjacent to the five-county San Francisco area, have been recently added to the SEER Program; however, data from these registries are not included in the analysis presented here.

Mortality data were obtained from the National Center for Health Statistics for the entire United States and population estimates by county from the Census Bureau, the latter being required for the calculation of cancer incidence and mortality rates.

In calculating incidence/mortality rates for age ranges, e.g., 20-39, the rates are age-adjusted within the designated range using weights from the 1970 United States Standard population for the 5-year age groups included in the range.

Results

Proportion of Breast Cancers Diagnosed at Younger Ages

Fig. 1 presents the cumulative distribution of breast cancers occurring in women during the period 1987-1989 by age at diagnosis in the SEER areas. Only 6.5% of the breast cancers were diagnosed in women under age 40, and 21.8% were diagnosed before the age of 50. Applying the 6.5% to the 183 000 breast cancers expected to be diagnosed in women in the United States during 1993 (2) indicates that approximately 12 000 breast cancers will be diagnosed in women under the age of 40.

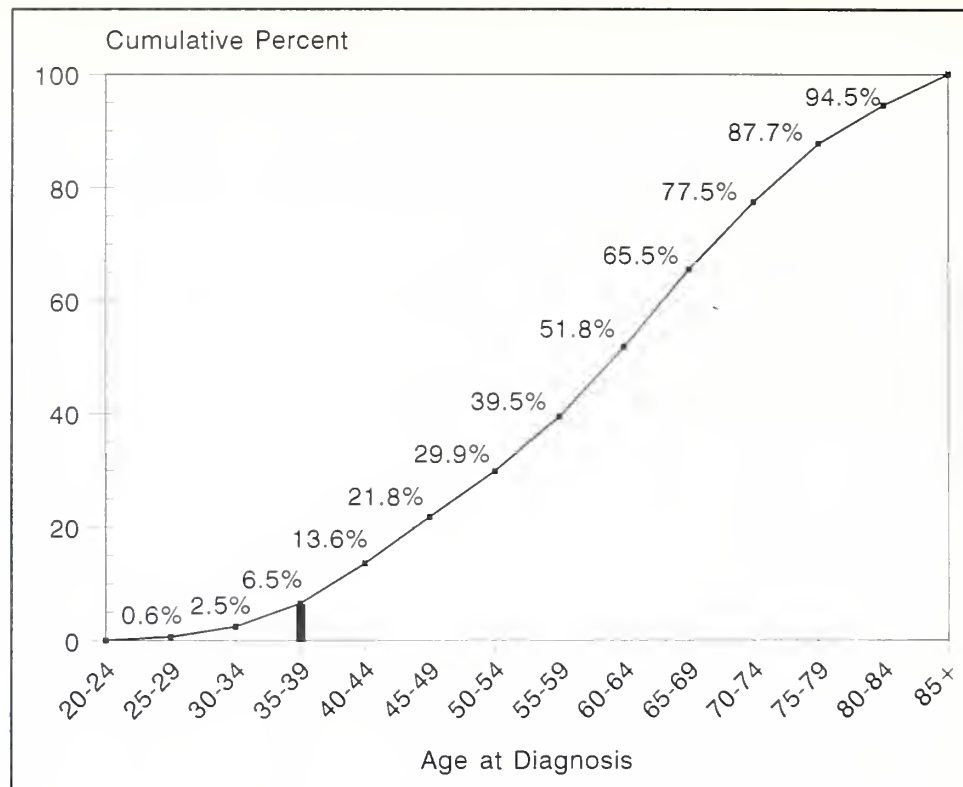
Probability of Developing Breast Cancer

The probability of developing cancer can be calculated up to a specified age or for an entire lifetime. It is a useful statistic to consider, particularly in regard to the study of a rare event like

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Fig. 1. Cumulative distribution of breast cancer diagnoses by age for the period 1987-1989.



the diagnosis of breast cancer in young women, because it puts the occurrence of such an event in a proper perspective. The method used here to calculate the probability of developing breast cancer was developed by Feuer et al. (3).

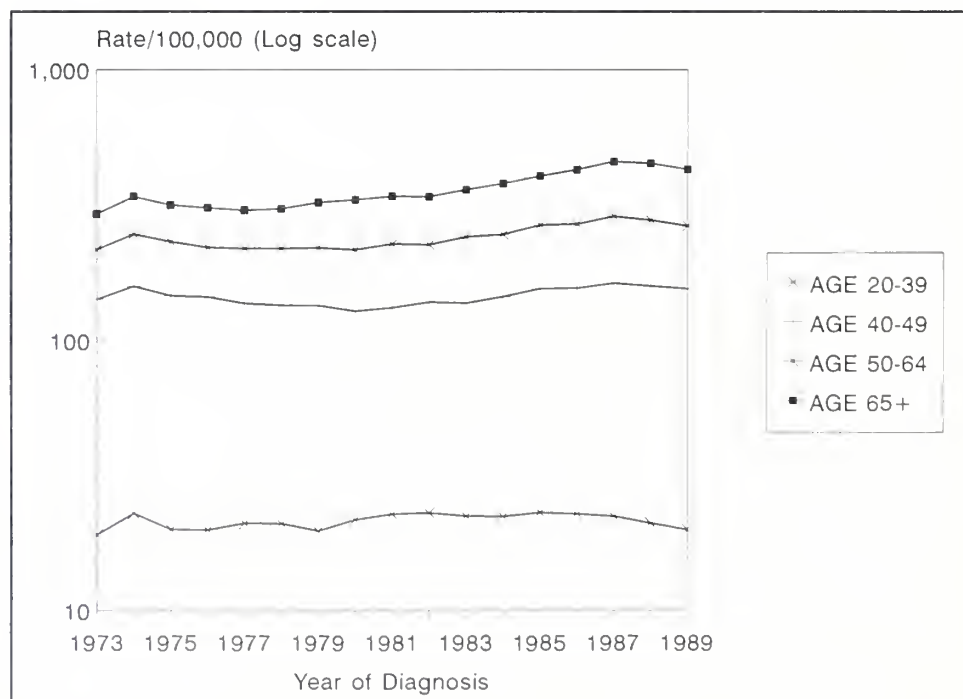
The lifetime probability of developing breast cancer varies somewhat by race, being .13 in white women, i.e., 13 of 100 women followed from birth develop breast cancer over their lifetime versus .09 in black women. Prior to age 50, these prob-

abilities do not differ appreciably by race. The probability of developing breast cancer prior to age 50 is .02 and prior to age 40 is less than .01.

Incidence/Mortality Trends

Breast cancer incidence trends by age are presented in Fig. 2. The log scale is used here and in some subsequent graphs, meaning that lines which are parallel have the same proportional

Fig. 2. Trends in invasive breast cancer incidence rates for following age groups: 20-39, 40-49, 50-64, 65+.



rate of change over the X axis, which is calendar year in this case. It is of interest to note that the effect of increased public awareness associated with the diagnosis of breast cancer in 1974 in two prominent public figures, Happy Rockefeller and Betty Ford, had roughly the same proportional impact in all of the age groups, i.e., the lines connecting the 1973 and 1974 rates appear to be parallel across all of the age groups, except for the youngest age group where the line appears to be steeper. The trends of the rates in the three age groups 40 and older have an increasing slope for the period 1982-1987, with the slope for the oldest age group appearing to be the steepest, indicating a faster annual rate of increase as compared to the other two groups. Beginning in 1987, there appears to be a leveling off, if not a decrease, for the rates in these age groups. This recent change in the incidence trend is not likely due to chance variation.

During the 1980s up to 1987 when the incidence was rising in the older age groups, there was little change in the age group 20-39 after a small jump at the beginning of the decade (Fig. 2). Since 1987 the trend has either not changed or is decreasing.

During the conference, a number of individuals indicated that it was their feeling that there has been an increase in the number of young women getting breast cancer because doctors were reporting more diagnoses in younger women. Since any increase in reported breast cancer diagnoses in younger women was not likely due to an increase in the incidence rates, it was of interest to assess the change in the size of the young female population over time. Fig. 3 presents estimates of the total female population by age for calendar years 1970, 1980, and 1990. It can be seen that, over this 20-year period, there has been a dramatic increase in the number of women in the 20-39-year-old age range. Applying the age-specific female breast cancer incidence rates from the SEER Program to the 5-year age groups in the age range 20-39 for the three calendar years yields the following numbers of cancers diagnosed in this age range: 5120 diagnosed in 1970; 7800 diagnosed in 1980; and 10 050 diagnosed in

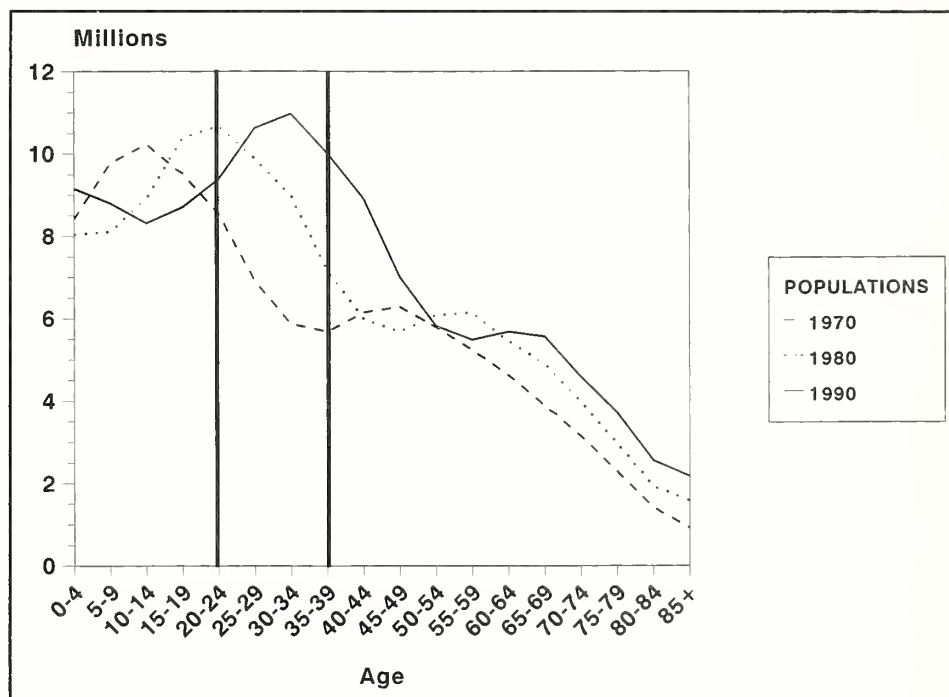
1990. For 1970, 1973 SEER rates were used, since the SEER Program was not established until 1973. Clearly, there has been a large increase in the *number* of women diagnosed with breast cancer at ages 20-39. However, the increase in numbers is primarily due to the increase in the size of the young female population, since the incidence rates have remained relatively constant over the period (Fig. 2).

Reasons for the Increase in Incidence at Older Ages

While the focus here is on breast cancer in younger women, it is of interest to consider possible reasons for the increase in incidence in the older age groups that occurred during the 1980s. Based on survey data, the rate for the use of mammography for breast cancer screening, i.e., the percent of women without symptoms who had had a mammogram within the last year, has increased from 5% to 10% at the beginning of the decade to more than 20% in 1987 in women aged 40 and above (4).

If it is assumed that in situ breast cancers, as well as localized invasive cancers <2 cm in diameter, are on the average slower growing than other breast cancers, then, due to a phenomenon known as length-biased sampling (5), these early cancers should be preferentially detected at screening and diagnosed at an earlier point in their natural history. The interval between the time at which a cancer is detected at screening and the time at which it would have been diagnosed clinically is referred to as lead time (5). Over the period that the use of mammography was increasing, the incidence of breast cancer in a given calendar year would include all those cancers expected to be diagnosed in the absence of early detection plus those cancers diagnosed early that would have otherwise been diagnosed at a later time. Eventually, the increase in incidence should begin to wane because of the number of cancers removed from the total pool of breast cancers in a given calendar year due to an earlier diagnosis in a previous calendar year. The dynamics of such a change in incidence would be governed by such things as the rate of increase

Fig. 3. Total U.S. female population by age and calendar year.



in early detection and the amount of lead time associated with the cancers diagnosed early.

Fig. 4 presents trends in the incidence rates by age for in situ and localized invasive tumors ≤ 2 cm in diameter for the period 1983-1989. As expected, rates increase for these two groups in patients 40 years and older at diagnosis, although only through 1987. After 1987, the rates level off. For women 20-39 years of age, there is little change in the rates for localized invasive cancers ≤ 2 cm in diameter and a smaller increase in the rate for in situ. Rates for all other invasive cancers (not shown) in all age groups changed very little during this period. It is of interest to note that the incidence of in situ cancers does not increase with age the way the rate for small invasive cancers does; in fact, there is no increase by age in the incidence of in situ cancers above age 50.

These observations provide indirect evidence that early detection played a major role in the increase of breast cancer incidence that occurred during the early 1980s. An alternative possibility is that temporal changes in risk factors selectively affected the incidence of early-stage breast cancers. We are not aware of evidence supporting this possibility.

Subsequent to 1987, it is of interest to note that in conjunction with the leveling off of the incidence rates in the older age groups, the reported proportion of women who had had a mammogram within the last 12 months roughly doubled between 1987 and 1990. These data were collected as part of the National Health Interview Survey that is conducted annually by the National Center for Health Statistics. Thus, trends in mammography utilization and breast cancer incidence during the period 1987-1990 present something of a conundrum. Efforts to understand why breast cancer incidence did not continue to increase are currently underway (6). Part of the explanation rests with the dynamics of the interrelationships between lead time, screening rates, and baseline incidence trends as described by Feuer and Wun (7).

Incidence/Mortality Patterns by Race

There are some interesting contrasts between breast cancer incidence and mortality patterns for blacks and whites. Mortality rates given here are for the total United States. Fig. 5 presents black/white differences in incidence and mortality by age for the period 1987-1989. The incidence of breast cancer is higher in blacks up to age 40, and breast cancer mortality is higher in blacks up to age 65. Differences in incidence and mortality by race have existed for several years among younger women (Fig. 6).

Stage at Diagnosis and Survival Patterns by Race

The staging system used by the SEER Program to classify cancers consists of the following categories along with their definitions: localized—invasive malignant neoplasm confined entirely to the organ of origin; regional—malignant neoplasm that has extended beyond the limits of the organ of origin directly into surrounding organs or tissues, involves lymph nodes by way of the lymphatic system, or has both regional involvement and involvement of regional lymph nodes; distant—malignant neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis (e.g., implantation or seeding) to distant organs, tissues, or via the lymphatic system to distant lymph nodes; and unstaged—insufficient information for staging purposes. This system can be applied to patients diagnosed in all years since the beginning of the SEER Program.

Fig. 7 presents the percent of tumors that were localized to the site of origin at diagnosis by age and race. For breast cancers diagnosed in women under the age of 40, there is very little difference in this percent by race or age group. The percent localized decreases for blacks in the older age groups, which is somewhat surprising since screening recommendations apply primarily to women 50 and older. However, other factors could

Fig. 4. Trends in breast cancer incidence rates for in situ and localized invasive tumors ≤ 2 cm in diameter for the following age groups: 20-39, 40-49, 50-64, 65+.

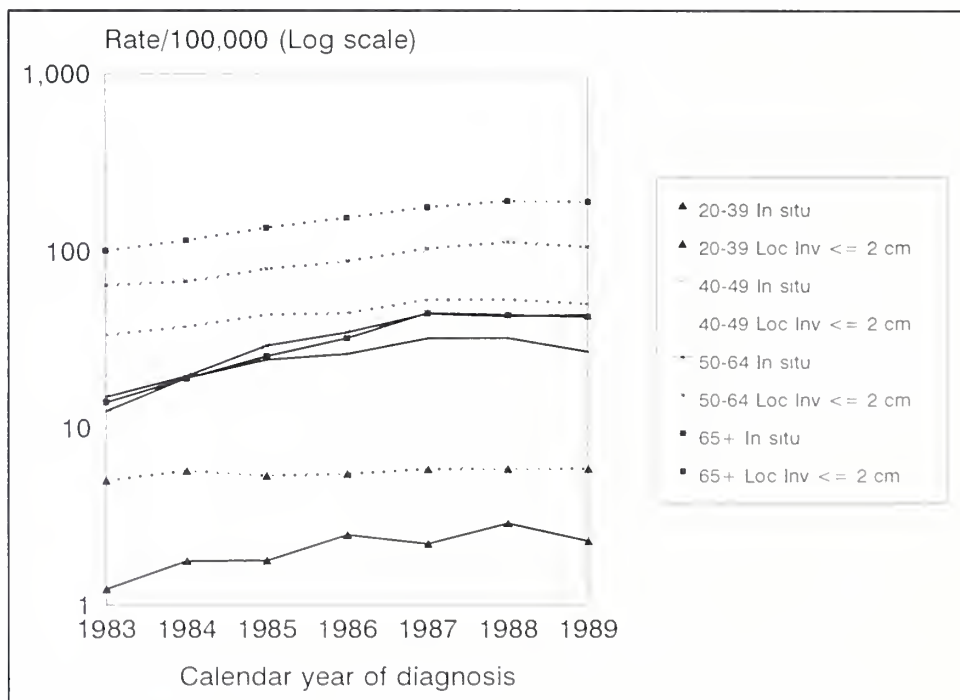


Fig. 5. Age-specific female invasive breast cancer incidence rates and age-specific female breast cancer mortality rates (total, United States) by race.

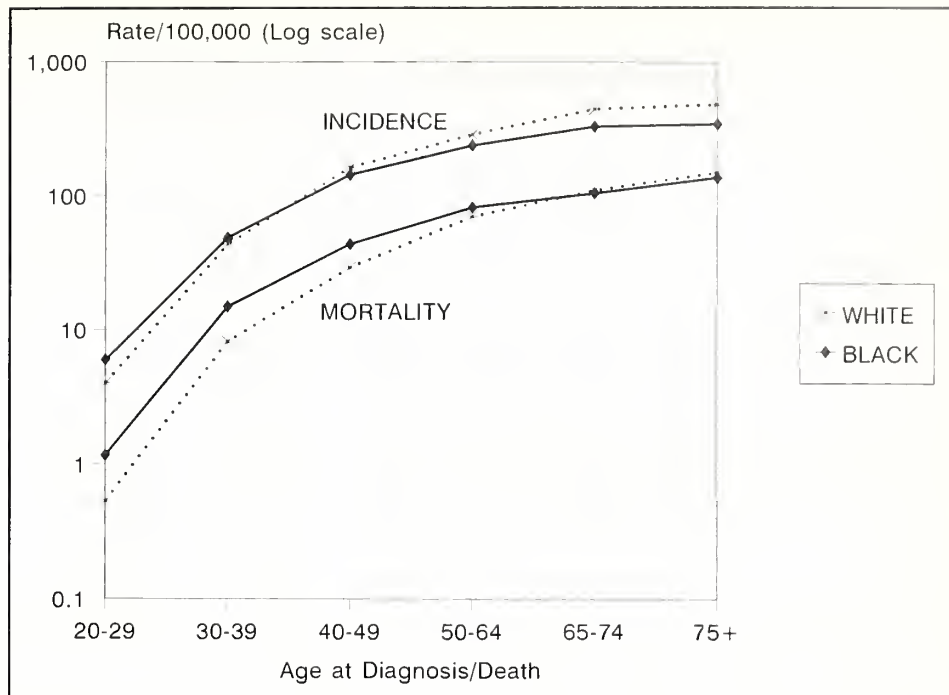
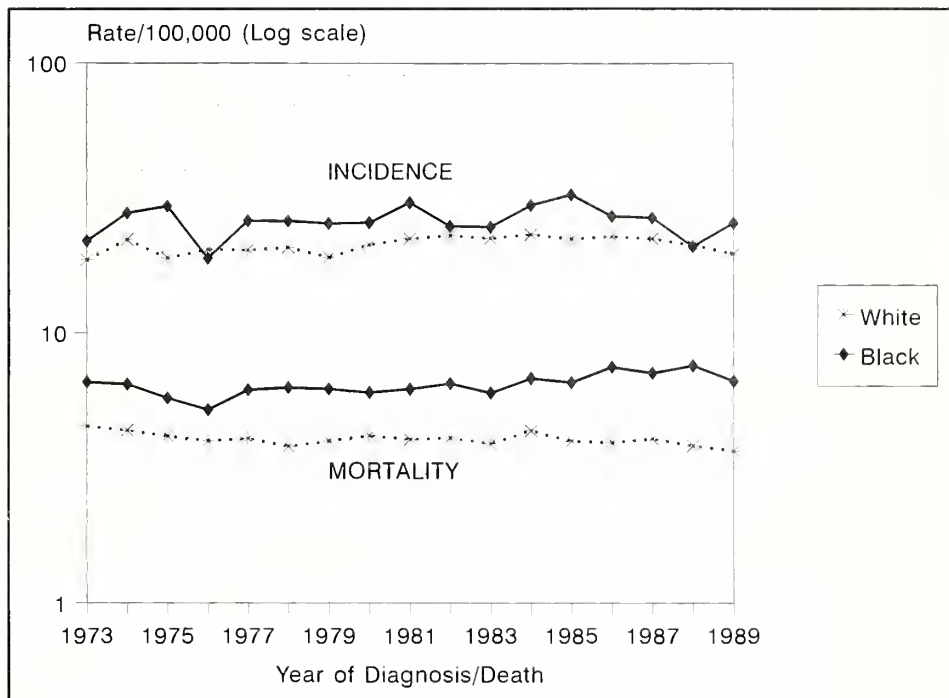


Fig. 6. Female invasive breast cancer incidence rates and female breast cancer mortality rates (total, United States) for the age group 20-39 by race and calendar year.



be operating, e. g., at older ages, breast cancers in black women may be more aggressive than those in whites.

Fig. 8 presents 5-year relative survival rates by race and age for all stages combined. The rates improve somewhat among whites up to age 50, whereas there is no evidence of an effect of age on survival among blacks. For the age group 20-29, the difference between the rates is not statistically significant and there are no differences in survival by stage (not shown). For women 30 and older, survival for whites by stage was better than that for blacks in all cases, except for patients 40-49 years old at diagnosis with distant disease, in which case survival for blacks

was only little better than that for whites; however, the difference was not statistically significant (not shown).

Second Cancer Risk (Incidence)

The risk of subsequent cancers in women with a first invasive breast cancer also varies by age at diagnosis of the first breast cancer and, therefore, is considered here. Other reasons for analyzing second cancer risk associated with female breast cancer include 1) obtaining clues about the etiology of selected second cancers since, if they occur in excess, this may indicate the presence of risk factors in common with breast cancer, and

Fig. 7. Percent of invasive breast cancers diagnosed as localized by race and age for the period 1975-1984.

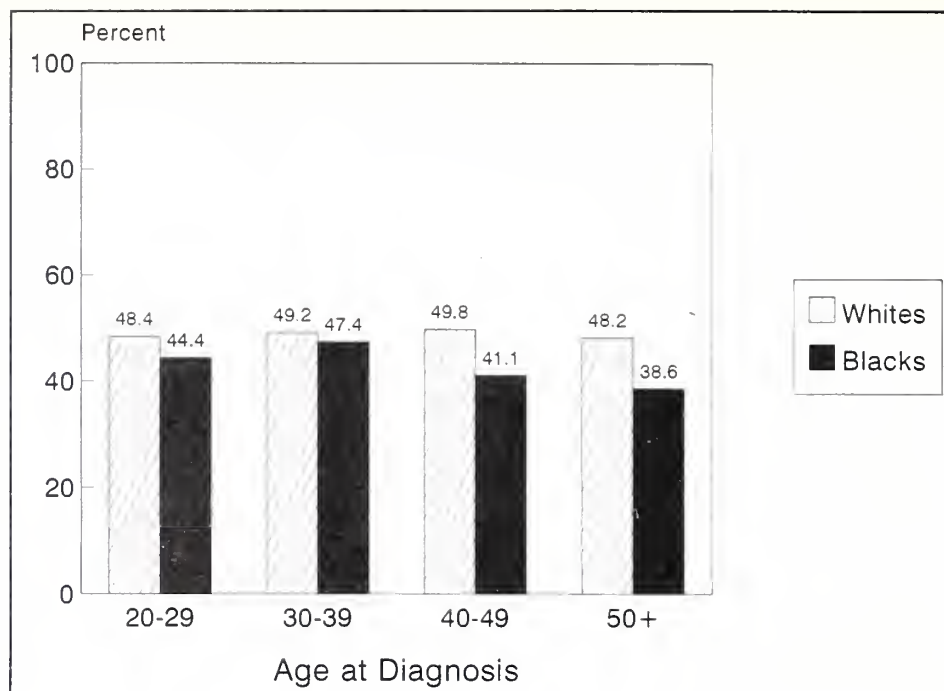
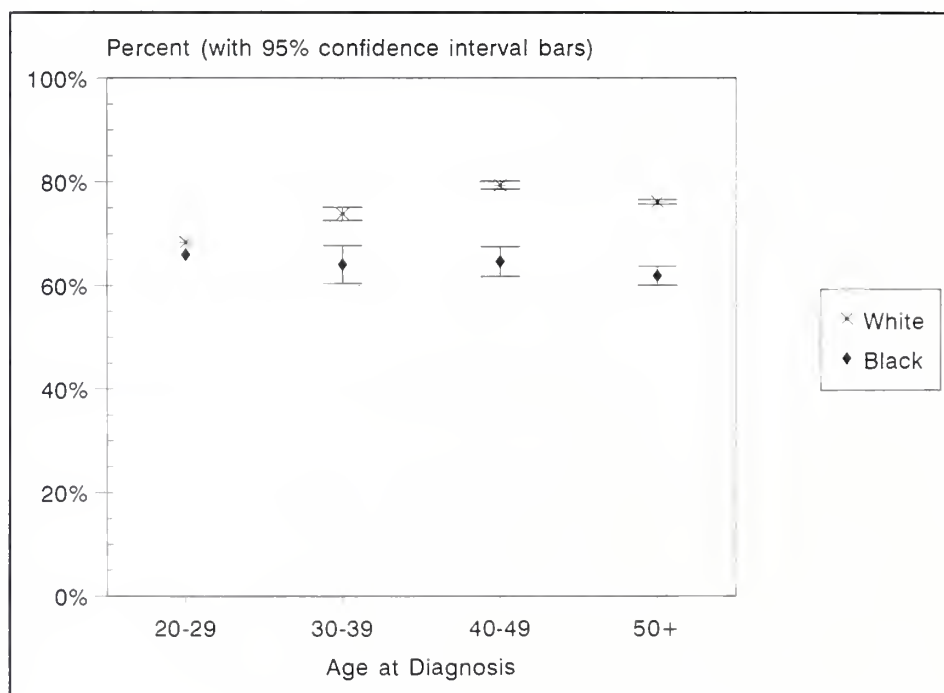


Fig. 8. 5-year relative rates by race and age for the time period 1975-1984. Relative survival rates not significantly different in 20-29-year age group.



2) identifying second cancers that may have been caused by treatment of the first breast cancer. Clinically, it is of interest to know which cancers occur in excess in order that patients be monitored over time for the occurrence of such malignancies.

Excess risk and relative risk of various second cancers per 100 000 person-years were calculated. The person-years at risk for a second cancer is defined to be that time starting 2 months after diagnosis of the breast cancer and extending to the first of the following events: date of diagnosis of any second cancer, date of last follow-up, date of death, or December 31, 1989. Women who survived less than 2 months after diagnosis were excluded from

the analysis. The expected numbers of second cancers were calculated by multiplying cancer site-age-calendar year specific incidence rates, as routinely reported by SEER, by the person-years at risk in each cancer site-age-calendar year category. The numbers were then summed to arrive at the total numbers of expected second cancers.

The size of the first breast cancer cohorts by age were as follows; <20 (19 women), 20-29 (1431 women), 30-39 (11 002 women), 40-49 (26 590 women), and 50+ (127 501 women). A factor limiting this analysis is the fact that the more recently diagnosed cases made a lesser contribution to person-years at

risk of second cancers, since they could only be followed through the end of December 1989.

Findings were as follows. Breast cancer patients aged 20-39 at diagnosis were at a significantly increased risk of developing a second invasive cancer of the breast, ovary, and lung. Each of these second cancers showed a consistent pattern of being elevated when the data were analyzed as two cohorts: those patients with a first invasive breast cancer diagnosed during the period 1973-1979, and those patients with a first invasive breast cancer diagnosed during the period 1980-1989. Second leukemias were also found in excess, but have been shown in previous reports (8,9) to be related to the radiotherapy and chemotherapy given to treat the initial breast cancer and, therefore, will not be reviewed here.

An excess of second invasive breast cancers is to be expected, but the pattern of increased risk in younger women is of interest. In the age group 20-29, the risk of a second invasive breast cancer was 29.8 and was related to time from diagnosis of the first breast cancer (Table 1). Risk decreased from 79.6 during the first year after diagnosis to 15.4 10+ years after diagnosis. In general, the second breast cancer excess decreased with age and time from diagnosis for women with a first breast cancer diagnosed under the age of 50. For women with a first invasive breast cancer diagnosed after the age of 50, the relative risk was 1.8 and was not related to time from diagnosis.

Second cancers of the ovary and lung were found to be elevated in women with a first invasive breast cancer diagnosed

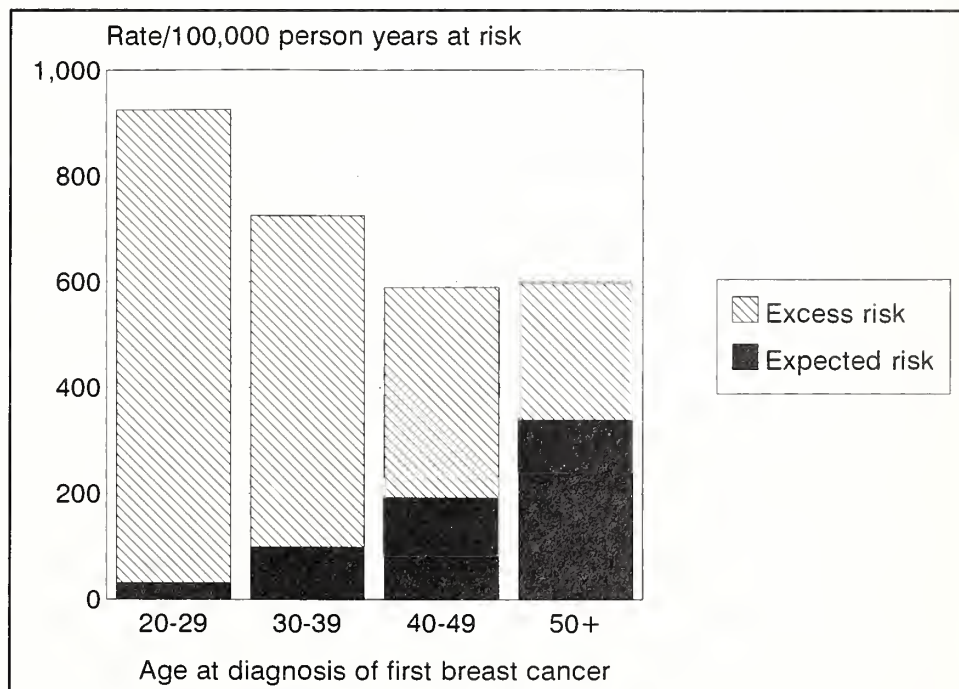
Table 1. Risk of second *invasive* cancers following a first *invasive* breast cancer diagnosed during the period 1973-1989 by age at diagnosis of the first breast cancer*

Second cancer site	Age at diagnosis	Time from diagnosis, y									
		Total		<1		1-4.9		5-9.9		10+	
		O/E	O	O/E	O	O/E	O	O/E	O	O/E	O
Breast	20-29	29.8	67†	79.6	10†	45.9	33†	18.1	16†	15.4	8†
	30-39	7.4	403†	10.9	55†	10.4	233†	5.2	97†	2.1	18†
	40-49	3.1	869†	4.3	138†	3.5	417†	2.5	217†	2.2	97†
	50+	1.8	3645†	1.7	525†	1.9	1890†	1.6	919†	1.6	311†
Ovary (including tubes)	30-39	4.3	25†	3.5	2	3.3	8†	5.4	11†	3.9	4†
	40-49	2.1	80†	2.3	9	2.2	35†	2.3	28†	1.3	8
	50+	1.2	344†	1.4	63†	1.1	165	1.2	93	0.9	23
Lung	30-39	2.1	16†	2.2	1	3.2	8†	1.7	5	1.0	2
	40-49	1.6	128†	0.9	5	1.6	45†	1.5	42†	1.9	36†
	50+	0.9	781	0.7	83†	1.0	382	0.9	211	1.3	105†

*Observed number of second cancers (O) divided by the expected number (E) with the observed number given in parentheses. Included in the calculation of the risks were women who survived 2 months or more following the diagnosis of their first invasive breast cancer.

†Risk significantly different from 1.0 ($P < .05$).

Fig. 9. Expected risk and excess risk of a second invasive breast cancer following a first invasive breast cancer diagnosed during the period 1973-1989.



at ages 30-49 (Table 1). The risk of a second ovarian cancer was highest in the age group 30-39. The relative risks for both cancers were not related to time from diagnosis. The finding of elevated risks for second breast and ovarian cancers in young women with a first breast cancer is consistent with the identification of a genetic marker, which has been reported to be associated with the occurrence of breast and ovarian cancers at a very young age (10).

Excess risk (absolute risk) of developing a second invasive breast cancer was calculated by age at diagnosis of the first invasive breast cancer (Fig. 9). This risk was quite high in the 20-29 age group (893.8 per 100 000 person years at risk). The rate decreased with increasing age at diagnosis of the first breast cancer, but remained high relative to the expected rate.

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Risk Factors for Breast Cancer in Younger Women

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Epidemiologic studies of breast cancer that have included younger, premenopausal women in their populations have found that factors that predict altered risk of breast cancer after menopause can have different or even reversed effects before menopause. We have reviewed the literature on risk factors for breast cancer and their associations with breast cancer in general, and compared the risks for younger women with those for women diagnosed at older ages. Race, parity, and large body size are factors that may have opposite effects on breast cancer risk in younger and older women. Other factors of particular significance in the etiology of early-onset breast cancer include a late age at first birth, never having lactated, oral contraceptive use at early ages or of long duration, a family history of breast cancer, and a history of proliferative benign breast disease. [Monogr Natl Cancer Inst 16:15-22, 1994]

Most epidemiologic studies of risk factors for breast cancer have been conducted in populations of older, largely postmenopausal women. Since only 14 of every 100 women diagnosed with invasive breast cancer are under age 45 (1), it has been more difficult to accumulate large numbers of young breast cancer cases for study. The age distribution of breast cancer incidence in women under age 45 can be seen in Table 1. Studies that have included younger, premenopausal women in their populations have found that factors that predict altered risk of breast cancer after menopause can have different, or even reversed, effects on the risk of premenopausal breast cancer (2-4). This crossing over of risk factors has prompted the question of whether premenopausal and postmenopausal breast cancer are not two distinct disease entities (5,6).

The incidence of breast cancer in women under 50 years of age in the United States has increased by 5% among whites and 10% among blacks over the period 1973-1989 (7). The increases are much smaller than those observed over the same time period in women over 50, in whom the incidence for all races increased by nearly 30% (7). These results, based on reports from all U.S. Surveillance, Epidemiology, and End Results (SEER) registries, differ from those of some earlier reports from western Washington state (8), Sweden (9), and Denmark (10), which described much larger increases in breast cancer incidence in younger age groups from the early 1970s to mid-1980s. Changes in the distributions of known and suspected risk factors for breast cancer, in particular, older age at first birth, reduced parity, and greater prevalence of oral contraceptive use and in-

Table 1. Age distribution of invasive breast cancer in women under age 45*

Age, y	% among SEER, 1973-1987
20-24	0.7
25-29	5.4
30-34	15.9
35-39	30.6
40-44	47.4

*14 of every 100 women diagnosed with breast cancer are under age 45.

duced abortions at young ages, have been proposed as possible explanations of these incidence trends (8,10,11).

The relations of chronologic age and of menopausal status, "breast tissue age," and other measures of reproductive age to breast cancer incidence have been described and modeled (12-15). Generally, incidence rates of breast cancer increase very rapidly with age until menopause or around age 50, then continue to increase with age, but more slowly. It can be difficult to assess whether differences in the effect of some breast cancer risk factors in younger and older women are related to chronologic age or menopausal status, since both can independently affect women's susceptibility to breast cancer, but are also correlated with each other. Often, though, a biological rationale exists for expecting that the effects of a particular factor on breast cancer risk may be modified by either hormonal changes associated with menopause or duration of time since some event of interest.

In this paper, we have reviewed the literature on risk factors for breast cancer and their associations with breast cancer in general and compared the risks for younger women with those for women diagnosed at older ages. We did not attempt an exhaustive review of the breast cancer literature, but rather chose to emphasize large and recent epidemiologic studies and those which either focused on younger or premenopausal women or stratified their analyses by age or menopausal status. These studies use different age classifications of "younger" women and various age- and menses-based definitions of menopausal status. We have not distinguished between these categorizations

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See "Notes" section following "References."

when making generalizations to "younger" or "premenopausal" populations.

Accepted Risk Factors in Older/Postmenopausal Women

Some risk factors for postmenopausal breast cancer have been recognized for many years and are often regarded as "accepted" in the literature. Among these are the reproductive factors of nulliparity and low parity, late age at first pregnancy, and young age at menarche (16,17). Obesity or other measures of large body size are also thought to increase risk after menopause (16,17). Moderate and high levels of alcohol use have been shown with some consistency to be risk factors (16,17). Family history of breast cancer and previous benign breast disease also predict elevated risk (16,17). Demographic variables such as white race, being married, and measures of high socioeconomic status have also been associated with being at high risk for postmenopausal breast cancer among women in the United States (18,19).

Table 2 compares the magnitude of the relative risks associated with these and other risk factors for breast cancer between pre- and post-menopausal women.

Race

The incidence of breast cancer in black women younger than 40 is higher than in white women under 40, whereas the opposite is true for women over 40 (19,35). Furthermore, the observed increase in incidence of breast cancer among younger women from 1973 to 1989 has been twice as large among blacks as whites (7).

Several studies of breast cancer in black women in the United States have identified risk factors for premenopausal and postmenopausal breast cancer that are the same as those

reported for white women (18,36,37). This evidence suggests that the etiology of the disease is similar between blacks and whites.

Krieger (19) used census block group data to stratify age-specific black and white breast cancer rates by social class in a 1990 study. Socioeconomic status was shown to be a strong effect modifier of the age-specific relationship between race and breast cancer incidence: the excess risk for black women under 40 was seen only in higher socioeconomic status groups, whereas the excess risk among white women over 40 was seen only in the lower socioeconomic status groups.

The excess risk of breast cancer in young black women remains largely unaccounted for. Younger age at menarche (35) and higher frequencies of induced abortions and oral contraceptive use at early ages (12,19) among black women have been suggested as possible explanations. These factors have been shown in the literature to be associated with increased risks of breast cancer in younger women; however, black women have not been included in most studies. Reproductive characteristics such as earlier age at first birth (22,37-40) and higher parity among black women might be expected to protect them (38-41), though parity is likely to be a stronger determinant of postmenopausal than premenopausal breast cancer (23,35,42). The strong effect of social class on black/white breast cancer incidence rates may point to differential exposures to some unrecognized exogenous carcinogens (43).

Reproductive Factors

Most epidemiologic studies of the effects of reproductive factors on breast cancer risk have confirmed the findings that younger age at menarche and late age at menopause are associated with an increase in risk (16,17,20,21,42). An increased risk with late age at first birth and low parity or nulliparity have also been generally agreed upon (16,17,38,40,42).

Perhaps because these menstrual and reproductive events are considered such well-established risk factors for breast cancer, it is not always considered whether their effects differ according to age or menopausal status. Some studies have reported that the protective effect of a late age at menarche on breast cancer risk appears stronger in younger women (2,4,44,45), but an equally consistent finding is that the effect does not differ by age at diagnosis (20,46-48). For instance, Brinton et al. (20) found a relative risk of breast cancer for women whose age at menarche was 15 or later compared with less than 12 years of 0.82 for those under 45 years old and 0.78 for those 45 and older. It was observed by Trichopoulos et al. (21) in 1972, and was supported by more recent studies (4,20,46), that early menopause seems to confer protection against breast cancer that is of long duration and of reasonably similar magnitude across strata of age at diagnosis.

Though the influence of menstrual events on breast cancer risk appears similar for younger and older women, there is considerable evidence that the effects of parity and age at first birth on breast cancer risk vary with age. The generally protective effect of parity may be less strong (37) or even associated with an increased risk relative to nulliparity (4,23,49,50) among younger women, though some have not found such a difference

Table 2. Comparison of risk factors for breast cancer in younger and older women*

Risk factors (ref. no.)	Relative risk in younger women	Relative risk in older women
Race, black versus white (19)	+	-
Early age at menarche (20)	+	+
Late age at menopause (21)	+	+
Late age at first birth (22)	++	+
Parity (22,23)	+	-
History of lactation (24-26)	-	?
Induced abortion	?	?
Alcohol exposure (27)	+	+
Smoking exposure (28,29)	0	0
Dietary fat	?	?
OC use (early or long) (30)	+	0
Family history of breast cancer (31)	++	+
Proliferative benign breast disease (32)		
Without atypia	+	+
With atypical hyperplasia	+++	++
Large body size (33,34)	-	+

*+ = estimated relative risk of 1.1-1.9; - = estimated relative risk of 0.5-0.9; ++ = estimated relative risk of 2.0-4.0; ? = evidence insufficient or too conflicting to estimate risk; 0 = estimated relative risk of 1.0 (no association); +++ = estimated relative risk of >4.0.

(2,39,40,51). The apparent increased risk of breast cancer associated with late age at first birth seems to be stronger or only evident in younger women (2,37,40,41,45,48-50). In a 1991 report, Lund (22) reported relative risks of breast cancer for having a late (age ≥ 35) birth to be 2.58 among premenopausal women and 1.35 among postmenopausal women, though the corresponding rate differences for each group were equivalent. A few studies have not found this difference in effect with age or menopausal status (4,38,51).

The roles of lactation and spontaneous or induced abortions are more controversial. Although some studies have found no effect of lactation on breast cancer risk (24,38), others have found protective effects that may or may not become stronger with duration of breast-feeding (25,26,44,50,52-54). Most studies (4,25,26,50,52-54) that reported results in younger women have found a decrease in risk of breast cancer associated with lactation in this group.

Induced abortions have been associated with an increased risk of breast cancer in some studies (38,41,55-57), but had no effect on risk in other studies (2,4,44,53,57). Three studies of abortion and breast cancer risk that reported results in younger women observed an increase in risk for induced abortions, particularly before first live birth (55-57). Others have found no association or were inconclusive (4,53,57-59).

Alcohol

Although at least four large cohort studies and more than 20 case-control studies have addressed the question of an association between alcohol consumption and breast cancer, the evidence has been conflicting. A fragile consensus has emerged that there are increased risks of breast cancer associated with heavy and moderate levels of drinking. A meta-analysis of four cohort and 17 case-control studies by Longnecker et al. (27) in 1988 calculated a risk of breast cancer at an intake of 24 g of alcohol (approximately two drinks) daily of 1.4 (95% confidence interval [CI], 1.0-1.8) from case-control data and 1.7 (95% CI, 1.4-2.2) from follow-up data. Studies that examined past consumption, age at start of drinking, or ages of heaviest drinking tended to find that drinking at earlier ages was associated with a stronger effect than recent or current drinking (60-63).

Since the picture that emerges from the many epidemiologic studies of alcohol consumption and breast cancer is not clear, it is difficult to establish how this relationship might vary between younger and older women. In three case-control studies in younger (<55 years old) populations, including the Centers for Disease Control's Cancer and Steroid Hormone Study, no association with breast cancer was seen for moderate drinking (<14 drinks/week) (28,64,65), although one study found an association of 1.8 (95% CI, 0.87-3.8) for 14+ drinks/week (65). Of five studies that described results within multiple strata of age or menopausal status, two found a weaker association (61,66) and three found a stronger association (67-69) in younger/premenopausal women than in older/postmenopausal women.

Possible biological mechanisms for an effect of alcohol on breast cancer could include: 1) an effect on membrane permeability to potential carcinogens (70), 2) stimulation of prolactin release (71), 3) increase in lipid peroxidation leading to DNA

damage by free radicals (72,73), and 4) effect on liver function (74,75). Alternate explanations for the frequently observed association include confounding by socioeconomic status or some unmeasured factor.

Cigarette Smoking

The effects of cigarette smoking on breast cancer risk have not been established, despite the number of published studies that examine this association. Despite a hypothesized antiestrogenic effect of smoking (76) and occasional reports of a decreased risk of breast cancer in smokers (77), most epidemiologic studies have found no association (28,78-85). In some studies, smoking has been associated with a small increase in breast cancer risk (29,86,87). One study found a larger increase in risk for women who began smoking at younger ages compared to other smokers (87).

Of the many studies of breast cancer and cigarette smoking that present results for both premenopausal and postmenopausal women, there is no strong evidence to support a difference in effect between these groups. A 1988 study by Adami et al. (28) in Scandinavian women under 45 years shows no association between cigarette smoking and breast cancer.

Dietary Fat

The observation of large international differences in breast cancer rates that correlate well with national per capita fat consumption led epidemiologists to anticipate a causal link between dietary fat and breast cancer from the 1970s (88). This hypothesis seemed to be supported by data from immigrant studies (89) and experiments in animals (90,91), and interest in dietary fat has dominated the study of diet and breast cancer.

The epidemiologic evidence for an association between fat consumption and breast cancer incidence has not been strong. The bulk of the data from case-control studies is compatible with a modest positive association between fat consumption and breast cancer risk. In a 1990 meta-analysis of 12 case-control studies of this issue by Howe, et al. (92), the relative risk of breast cancer associated with total fat intake in postmenopausal women (highest quintile compared to lowest) was 1.46; for saturated fat, the relative risk was 1.57 (92). The meta-analysis showed little or no association of fat intake with breast cancer in premenopausal women.

Evidence from prospective cohort studies has been mostly negative. Results from both the Nurses' Health Study (93) and National Health and Nutrition Examination Survey (94) cohorts have demonstrated no association between fat consumption and breast cancer incidence in premenopausal or postmenopausal women. A 1991 follow-up study by Howe et al. (95) did show an increased risk of breast cancer with increased fat consumption in women of differing menopausal status that was of similar magnitude to that found in postmenopausal women in the case-control meta-analysis (92).

The relative risks observed in epidemiologic studies of fat consumption and breast cancer risk in both premenopausal and postmenopausal populations have been of modest size for even large increments in consumption. Findings reported by some re-

searchers of stronger effects in postmenopausal populations probably do not represent meaningful differences.

Oral Contraceptives

Many epidemiologic studies have been conducted to address the question of whether oral contraceptive (OC) use affects breast cancer risk. Several major review articles (96-98) and a meta-analysis (30) have summarized this literature and concluded that there is no overall association between OC use, even of long duration, and breast cancer. However, increased breast cancer risk with use of OCs has been observed in certain subgroups, such as women at low risk for breast cancer (96), nulliparous women (96), and, most consistently, in younger, premenopausal women (30,96-99).

Since the mid 1980s, increased risks of breast cancer of 20%-100% for 4 or more years of use have been found in most studies in women under 45 years (96,98). These risks seem to be most elevated among women who are of younger age at breast cancer diagnosis (30,96,97) and with longer duration of OC use at young ages (30,96-100). Only a few recent studies seem to contradict the finding of a positive association of OC use and breast cancer risk specific to younger women (101,102). Other major studies have published generally negative findings in the past, and more recently reported on new age-specific analyses that support an association in younger women to some degree (103,104). In a 1990 meta-analysis by Romieu et al. (30) of 27 case-control studies, the summary relative risk of premenopausal breast cancer was calculated to be 1.46 for 10 or more years of OC use.

It is not yet understood why an increased risk of breast cancer associated with OC use may be greatest in younger women. If the association is causal, an age-specific effect could be due to a different response to hormonal causes of breast cancer in premenopausal and postmenopausal women, as is suggested by other risk factors such as obesity. The results of several studies by Olsson et al. (105-108) suggest that early users of OCs who develop breast cancer have an altered tumor biology and a worse prognosis than nonusers. Another explanation is a cohort effect, with the youngest women in recent studies being the first to have used OCs at young ages for sufficient duration and with sufficient latency for an effect to be observed (30,100). If so, some effect of OCs may continue to be observed in this and subsequent cohorts as they age. Alternatively, OC use may act to promote growth of existing breast tumors, resulting in earlier clinical manifestation of disease in some women but not impacting lifetime risk of breast cancer (98).

Family History of Breast Cancer

Although most breast cancers are believed to be of a noninherited (sporadic) type (109), more than a quarter of all breast cancer patients have a family history of breast cancer in a first- or second-degree relative (31,110). A much smaller fraction of breast cancer cases are believed to have true hereditary breast cancer (110), that is, to have inherited a genetic mutation that caused them to be more susceptible to the disease. This fraction may be as low as 5% of all breast cancer patients, but may be as

high as 25% among women who are diagnosed with breast cancer before age 35 (111).

Since an inherited susceptibility to breast cancer increases the probability that breast cancer will occur early in life (111), younger breast cancer cases are more likely to have a family history of breast cancer (112,113), particularly of early-onset breast cancer (113). Lynch et al. (113) reported that in a series of women with breast cancer, those diagnosed at age 40 or less were 2.8 times more likely to have a positive family history of breast cancer (of any age) than those diagnosed at older ages. Furthermore, a family history of early-onset breast cancer was 23 times more common among the younger breast cancer cases than the older ones (113). Other studies seem to support that the association between a positive family history and breast cancer is stronger among those who were younger at diagnosis (31,114). It has also been shown that the younger a patient is when she is diagnosed with breast cancer, the greater the elevation in lifetime risk of breast cancer is for her relatives (31,115-117). In a recent report by Houlston et al. (115), the relative risk of breast cancer for the relatives of patients older than 55 at diagnosis was 1.57, for relatives of patients less than 55 it was 2.29, and for relatives of those under 45 it was 3.85.

Benign Breast Disease

It has been well demonstrated in a few large epidemiologic studies that women with proliferative benign breast disease have an increased risk of breast cancer, with the greatest elevation in risk among those with atypical hyperplasia. Relative risks of breast cancer associated with atypical hyperplasia in three studies were 3.0, 3.7, and 4.0, all statistically significant (32,118,119).

In studies that have examined the association of benign breast disease with development of breast cancer within strata of age or menopausal status, the magnitude of the relative risk for atypical hyperplasia has been doubled or more in younger or premenopausal women compared with older or postmenopausal women (32,118,120). London et al. (32) presented relative risks of breast cancer for different subtypes of benign breast disease within categories of age (<55 years old; ≥55 years old) and menopausal status. In this study, the relative risk for atypical hyperplasia in premenopausal women was 5.9; in postmenopausal women it was 2.3 (32). There was somewhat less variation in relative risk by age, with relative risks of 4.5 and 2.6 for younger and older women, respectively (32). The magnitude of increased risk for proliferative disease without atypia did not appear to differ by age or menopausal status (32).

Body Size

The observed effect of body size on breast cancer risk seems to differ by menopausal status. Studies that have examined this question have tended to find an increase in risk associated with greater body mass for postmenopausal women (33,34,121,122) and a decrease in risk with greater body mass for premenopausal women (33,34,123-125). These trends have been fairly clear and consistent, although the magnitude of the relative risks is modest in some studies. Among premenopausal women in the

Nurses' Health Study Cohort, the age-adjusted relative risks for increasing quintiles of Quetelet's index (a measure of relative weight calculated as weight in kg/[height in m]²) were 1.0, 0.9, 0.9, 0.8, and 0.6. The test for trend was highly significant (125). In this study, there was no association between body mass and breast cancer among postmenopausal women (125).

Studies of the associations between changes in body mass or body mass at different times in life and breast cancer incidence have found that these relationships also vary with age or menopausal status. In 1985, Lubin et al. (121) reported that premenopausal breast cancer patients had gained significantly less and postmenopausal breast cancer patients had gained significantly more weight from age 18 to "most of adult life" than control women. A 1988 case-control study by Le Marchand et al. (34) found a strong negative association between adolescent body mass and premenopausal breast cancer, independent of any effect of adult body mass. No clear association between adolescent body mass and postmenopausal breast cancer was found in this study (34).

Two 1990 studies, one cohort (126) and one case-control (127), reported that women with a larger distribution of body fat in the abdominal area relative to other areas had a significantly increased risk of breast cancer independent of the effects of body mass. Ballard-Barbash et al. (126) reported that this effect was seen only in women over age 50 or postmenopausal women, although the number of younger, premenopausal women was small. The other study did not present results stratified by age or menopausal status (127).

The relationship between body size and breast cancer risk is clearly a complex one. The effects of body size on breast cancer risk may differ not only according to menopausal status but also with the distribution of fat and with body size at different times of life. The findings of reduced risk of breast cancer among obese premenopausal women and of a stronger association of adolescent body mass with premenopausal breast cancer are difficult to integrate with the theory that total energy intake, especially at an early age, is the unifying aspect of breast cancer etiology (128).

Occupational Environmental Factors

Although there have been some epidemiologic studies of occupation and cancer, few studies have focused specifically on an association between occupation and breast cancer or examined the effects of specific women's occupations (rather than very broad groups of occupations or husbands' occupations), except hairdressing. We found one case-control study (129) that presented relative risks of breast cancer for specific occupations separately for premenopausal and postmenopausal women. Among premenopausal women, relative risks of breast cancer of greater than 2.0 were found for those who had ever been in data processing, food processing, insurance, transportation, janitorial/housekeeping, or hairdressing occupations (129). There were no occupations associated with such a strong increased risk among postmenopausal women, suggesting that occupational risk factors may play a greater role in the etiology of premenopausal breast cancer (129). In general, however, it is difficult to determine that a specific occupation confers high risk of breast

cancer separate from the socioeconomic and lifestyle factors that are strongly correlated with occupation and hard to measure.

Diverse factors such as breast implants, hair dyes, coffee drinking, sunlight, electromagnetic field exposure, and pesticides are sometimes broadly classified as "environmental" exposures in the literature of breast cancer epidemiology. Most of these, with the exception of hair dyes and coffee (for which no increases in risk have been shown in younger or older women) (130-135), have not received sufficient study to determine whether any effects on breast cancer risk, if they exist, may differ by age or menopausal status.

Conclusion

Of all the factors that have received much research attention for their possible role in breast cancer etiology, some stand out as being of particular importance in younger or premenopausal women. Race (black versus white), parity, and large body size are two factors associated with increased risk in younger women that "cross over" or exert the opposite effect in older women, at around 40-50 years of age. A late age at first birth, never having lactated, oral contraceptive use at early ages or of long duration, and a history of proliferative benign breast disease with atypical hyperplasia are all associated with greater increased risks of breast cancer in younger than older women. Family history has special significance as a determinant of breast cancer risk in younger women, with the hope that a gene for early-onset breast cancer will soon be identified. An early menarche seems to exert equal influence on breast cancer risk at younger and older ages.

Future epidemiologic studies of breast cancer should strive to include younger and older women in their populations, stratify results by age and/or menopausal status at diagnosis, and explore critical time periods of past exposure, when possible. Studies of occupational and environmental exposures are sorely needed, and may be of particular relevance to young women who are most likely to be working and adolescent girls and children whose breast tissue may be unusually susceptible to carcinogenesis.

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Pathology and Heredity of Breast Cancer in Younger Women

Joseph N. Marcus, Patrice Watson, David L. Page,
Henry T. Lynch*

The pathology of early-age onset breast cancer is considered here from three perspectives: 1) benign proliferative disease, 2) the cancers themselves, and 3) familial and hereditary breast cancer. Hereditary breast cancer, a subset of familial breast cancer featuring a strong autosomal dominant pedigree pattern and multiple primary cancers, has a strong predilection for younger women, accounting for about one half of breast cancers under age 30. With respect to benign proliferative disease, the increased relative risk of breast cancer associated with proliferative disease with atypia, about fourfold to fivefold for all ages, is doubled by the presence of a family history of breast cancer and amplified by young age. With respect to the carcinomas, the relative incidences of medullary carcinoma and ductal carcinoma in situ are increased in young women, while lobular and tubular carcinomas are decreased. Invasive breast cancer is higher grade and more proliferative in younger women, as measured by thymidine-labeling index, DNA flow cytometric S-phase fraction, and proliferation-associated proteins. The increased fraction of ductal carcinoma in situ and higher grade invasive cancers may help to account, respectively, for increased recurrence rates with conservative therapy, and more aggressive natural history in younger women. Familial breast cancers show trends for increased medullary type, but the effect is not independent of age. Weak associations of family history with tubular carcinoma have been reported, but data for associations with lobular carcinoma in situ and invasive lobular carcinoma are conflicting. Hereditary breast cancer as a class has higher tumor proliferation rates, an effect independent of age. Knowledge of the pathology and biomarker characteristics of BRCA1 gene-linked hereditary breast cancers, which account for a substantial fraction of breast cancers in younger women, should shed light on the nature of the responsible gene(s) and guide approaches to therapy and prophylaxis. [Monogr Natl Cancer Inst 16:23-34, 1994]

Is breast cancer a different disease in younger women? This question could well be asked a bit differently: Is the *pathology* different in younger women? It is, after all, the pathology in the broad sense—stage, grade, DNA cytometry, and biomarkers like hormone receptors and oncogenes—that is associated with prognosis and guides therapy in breast cancer. What may at first appear to be an intrinsic tumor difference in young persons may in

fact be due to features that are a *function* of age. Age, in other words, may not be the independent variable.

In this review, we will look at the pathology of breast cancer in younger women, as well as the “pre-malignant” proliferative lesions that are linked to increased risk for breast cancer. Since a disproportionately large fraction of early-onset breast cancer is hereditary, attention will also be given to the pathologic features of familial and hereditary breast cancer, including our preliminary findings in the hereditary type.

According to the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program (1), 22.5% of breast cancer occurs in women before the age of 50 years, 7.3% before age 40, and 0.7% before age 30. Just what age defines a “younger” woman is to a large extent arbitrary. No consensus on any one cutoff value was reached at the National Institutes of Health conference that is the subject of these proceedings. In this review, we assess pertinent age-related pathology studies without attempting to select from among them on the basis of a predefined cutoff age.

Hereditary Breast Cancer in Younger Ages

Early-age onset breast cancer is remarkable for the increased incidence of positive family history in affected patients (2,3). However, positive “family history” is a loose term that can variably mean one or more first-degree relatives (mother, sister, or daughter) or second and higher degree relatives (grandmother, aunt, cousin, etc.) with breast cancer. Most studies in the literature on “family history” in breast cancer involve these definitions. We refer to such familial associations as *familial breast cancer* (FBC).

In contrast, we have defined *hereditary* breast cancer (HBC) as a subset of familial breast cancer cases in which breast and in some circumstances related cancers (e.g., ovary, as in the hereditary breast-ovarian cancer syndrome) have a high incidence and distribution in the pedigree that is consistent with an autosomal dominant, highly penetrant cancer susceptibility

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See “Note” section following “References.”

gene (4). Other factors that support the HBC classification include frequent early age at onset (premenopausal) and multiple primary cancers, including bilateral breast cancer. An example of an HBC family with many of these features is shown in Fig. 1 (5).

In the last several years, genetic linkage studies have bolstered the already strong evidence for HBC that had relied on pedigree, statistical, and epidemiologic data. A major breast cancer gene, BRCA1, has been localized to the q12-21 region of chromosome 17 for early-onset breast cancer (6) and for the hereditary breast-ovarian cancer syndrome (7). This gene(s) appears to account for some 45% of the former and perhaps 100% of the latter hereditary breast cancer syndromes (8).

Caution must be used with the terms "FBC" and "HBC," since either can masquerade as the other. In some cases, FBC can represent an HBC obfuscated by reduced penetrance of the putative gene(s), limited family history (particularly through the paternal lineage), and early death of key relatives (limiting informativeness of the pedigree). Conversely, HBC in certain circumstances may represent a chance occurrence, particularly in small families. The sine qua non for HBC diagnosis will be molecular genetic abnormalities (mutations in BRCA1 and other breast cancer genes yet to be discovered).

The predilection for early age of onset in HBC is shown in Fig. 2, which depicts 217 HBC individuals in 57 families ordered by mean age at breast cancer diagnosis (9). As can be seen, a substantial subset of families features extraordinarily early-onset disease, with tight ranges in onset ages within families. In this series, the age of onset of 22 of the 217 individuals (10.1%) was 30 years or less. If an incidence of HBC of 9% is accepted (10), then about 0.9% of all breast cancer is HBC with age of onset under 30. The incidence of all breast cancer under this age is 0.7% in the SEER data on 77 368 breast cancers (1) and is estimated as 1%-2% by Noyes et al. (11). Using the latter figure, the incidence of HBC in women 30 years of age or younger can then be conservatively estimated as 0.9%/2%, or about one half. This figure is somewhat less than the 85% carrier rate for an autosomal dominant susceptibility gene obtained by Williams and Anderson (12) for this age group, and somewhat greater than that obtained by Claus et al. (13,14). In the Claus et al. model, an autosomal dominant susceptibility gene is estimated to have a frequency of 0.33% in the

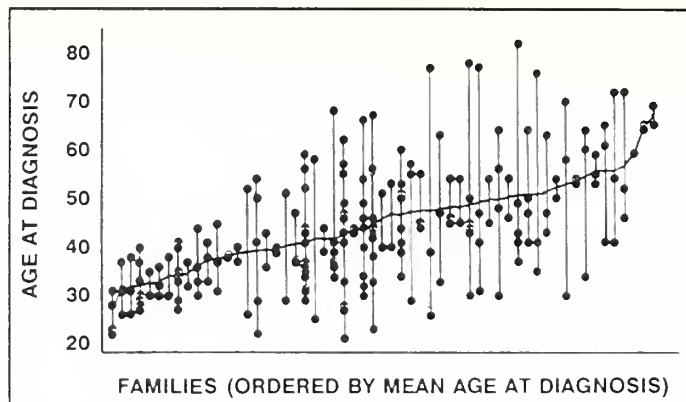


Fig. 2. Age at first diagnosis of breast cancer in 217 patients from 57 HBC families. Each vertical line = one family. The families are ordered by ascending mean age of diagnosis (connected by the upsloping line). Individual ages are shown by filled circles on the lines. Modified from Fig. 1 in Lynch et al (9), with permission of the authors and the J. B. Lippincott Co.

population and in the following age groups is associated with these percentages of breast cancers: 20-29 (36%); 30-39 (23%); 40-49 (14%); 50-59 (8%); 60-69 (5%); 70-79 (3%); and more than 80 (1%).

It is thus clear that a large fraction of early-onset breast cancer is hereditary, with estimates ranging from 36% to 85% for women aged 30 years and younger. Even the lower estimates indicate a high incidence of HBC in younger women. For this reason, the approach to the pathology of premalignant and malignant breast disease in younger women in the following sections will be two-pronged: we will look at age differences in breast pathology and also at the pathology of familial and hereditary subsets.

Proliferative Disease and Breast Cancer Risk

The breast, like other organ systems with dividing epithelia, has proliferative lesions that may be regarded as "pre-malignant," "preneoplastic," or perhaps most aptly, "nonobligate" precursors to cancer (15). Ewing (16), in his 1914 paper, "Precancerous Diseases and Precancerous Lesions. Especially in the Breast," had a thoroughly modern perspective when he wrote, "...certain pathological conditions are followed in a variable but high proportion of cases by carcinoma... but it should be emphasized that these diseases possess in themselves not a single essential element of the cancerous process. They are merely observed to precede and favor the development of cancer."

In modern parlance, these lesions are termed "proliferative disease," "hyperplasia" with and without atypia, and the like. They are recognized as risk markers that confer an increased relative risk (RR) of breast cancer that varies with the degree of hyperplasia and the presence or absence of specific atypical features that are similar to some found in *in situ* carcinoma (17,18). Until recently, the relation of benign breast disease to breast cancer risk has been controversial. Webber and Boyd (19) reviewed the literature up to 1984 and showed by meta-analysis that the best cohort studies to that time demonstrated a consistent increased breast cancer risk for varying histologic categories of benign breast disease. In 1985, Dupont and Page (17)

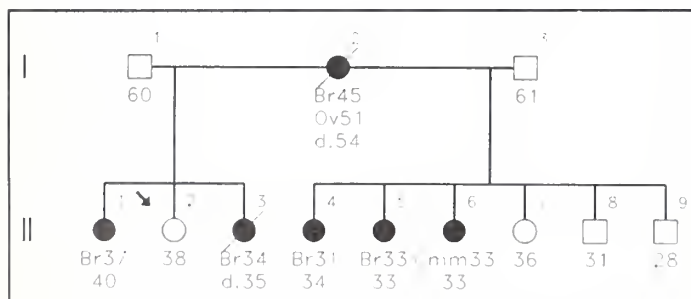


Fig. 1. A hereditary breast cancer family pedigree showing four breast cancer-affected women in two half-sibs, all at age less than 40; one other sib developed malignant melanoma. The mother died young with ovarian and breast cancer. Filled circles = women with histologically verified cancer; Br = breast cancer; Ov = ovarian cancer; Cmm = cutaneous malignant melanoma. Age at onset and current age or age at death (d.) are indicated next to cancer type. The pedigree is an updated version of one published earlier by Lynch et al. (5)

and Page et al. (18) published a study of breast cancer risk in 3303 women with benign breast disease who had long-term (median, 17 years) follow-up. In the study, the majority (70%) of benign biopsies were "nonproliferative disease," which included mild hyperplasias that did not exceed four cells in depth. This category conferred no increased risk of breast cancer. Moderate and florid hyperplasia of the usual type (Fig. 3) were termed "proliferative disease without atypia" (PDWA), comprised 27% of benign biopsies, and were associated with an only mildly elevated (1.5-fold to twofold) RR of breast cancer (Table 1). The third category, "proliferative disease with atypia," or "atypical hyperplasia" (AH), constitutes some 3%-4% of benign breast biopsies and includes the borderline lesions of atypical ductal or lobular hyperplasia (AH), which have some, but not all, of the features of in situ carcinoma. Most analyses (all of those in Table 1) do not separate atypical ductal and atypical lobular hyperplasias, which appear to have roughly equivalent risk for subsequent breast cancer (18), although further study of any differences would be warranted. The RR of breast cancer in the AH category is high, about fourfold to fivefold that of women who have had no breast biopsy (Table 1).

Atypical ductal hyperplasia has some, but not all of the features of ductal carcinoma in situ (DCIS), falling in between PDWA and DCIS. Its definition is a complex of architectural, spatial, and cytologic criteria, which will not be detailed here (17,18,20,21). While individual reports often do not provide photographs of the lesions under study, they reference earlier papers that in most instances provide illustrations for the pathologist.

Failure to uniformly observe the criteria for epithelial hyperplasias can result in diagnostic disagreement, even in experienced hands (22). When the criteria are rigorously observed, a good rate of diagnostic consensus can be attained by pathologists (23). A slight variation in the spatial extent criterion, presented in a recent, amply illustrated study of a large number of ductal hyperplasias, still results in a significant risk stratification when atypia is present (24).

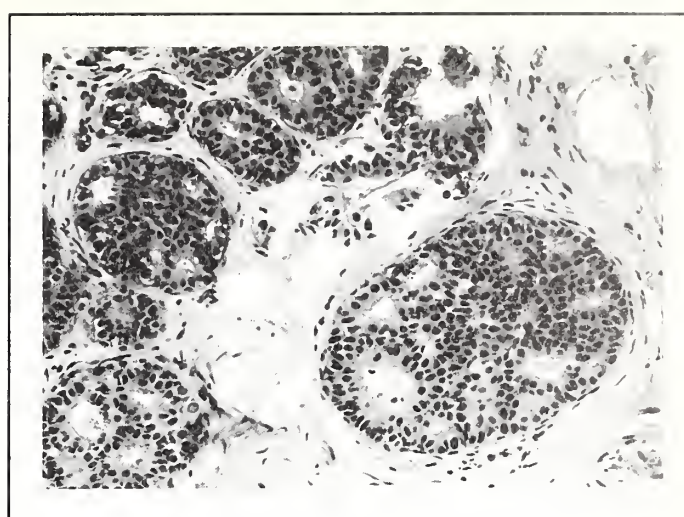


Fig. 3. This example of proliferative disease has suggestive atypical features but is still PDWA (see text). Centrally in the larger space cells are uniform in appearance but only approach the regular placement and rigid architecture of AH. The cells above the basement membrane bordering the lumen are different from the central cells, denying any possibility of a more worrying diagnosis (hematoxylin-eosin, $\times 200$).

The risk from AH is time-dependent, highest in the first 10 years after the biopsy (RR = 9.8), and less after 10 years (RR = 3.8) (25). Early first full-term pregnancy appears to lessen the risk from AH (26). DCIS is associated with a higher risk for invasive breast cancer. Even with microscopic foci of non-comedo DCIS, there is only a 25%-30% risk of recurrent carcinomas near the biopsy site after long-term follow-up (27,28), equivalent to an RR of subsequent invasive carcinoma of about 10-fold.

The Page and Dupont study (17,18) and its criteria became a key part of a Consensus Statement by the College of American Pathologists on histologic risk markers in benign breast biopsies (20). Several major studies have subsequently confirmed the conclusions of Dupont and Page and reinforced the Consensus Statement, with some differences in estimates of effect size (29-32) (Table 1). Varying RRs may be due to methodologic differences, including differing definitions of hyperplasias, presence

Table 1. Proliferative disease and breast cancer: increased risk in younger women and in women with a family history*

Investigators (ref. No.)	Age definition	FHx definition	RR† (95% confidence interval)					
			Total group		Younger age		Positive FHx	
			PDWA	AH	PDWA	AH	PDWA	AH
Dupont and Page, 1985 (17)	<46 y	1st degree	1.6 (1.3-2.0)	4.4 (3.1-6.3)	1.9 (1.2-3.2)	ND (ND)	2.1 (1.2-3.7)	8.9 (4.8-17)
Carter et al., 1988‡ (29)	<46 y	1st degree	1.9 (1.5-2.4)	3.0 (2.1-4.1)	2.70 (ND)	5.68 (3.0-10.6)	3.47 (ND)	3.93 (ND)
McDivitt et al., 1992 (32)	None	1st and 2nd degree	1.8 (1.3-2.4)	2.6 (1.6-4.1)	ND (ND)	ND (ND)	2.3 (0.8-6.2)	1.8 (0.3-9.3)
London et al., 1992 (30)	Premenopausal	1st degree	1.6 (1.0-2.5)	3.7 (2.1-6.8)	1.7 (0.8-3.0)	5.9 (2.6-13.2)	4.5 (1.1-18.4)	7.3 (1.1-50.1)
Dupont et al., 1993 (31)	Premenopausal	1st degree	1.3 (0.77-1.2)	4.3 (1.7-11)	1.6 (0.69-3.7)	12 (2.0-68)	2.6 (1.0-6.4)	22 (2.4-203)

*FHx = family history; PDWA = proliferative disease without atypia; AH = atypical hyperplasia; ND = not done.

†Denominators of risk are similar normal women except in two studies, where they are women with nonproliferative disease, adjusted for covariates [London et al. (30)], and women with nonproliferative disease and postmenopausal (for age RR) or with negative FHx (for FHx RR) [Dupont et al. (31)].

‡No central pathology review. PDWA and AH categories are less determinate in this study; they derive from other terms and as such are assumption-dependent.

or absence of central pathology review [absent in Carter et al. (29)], and varying lengths of follow-up (33) (shorter follow-ups may give increased RR).

The Page and Rogers criteria (17,18,20,21) that have guided many of the current studies are relatively conservative; they do not trigger a diagnosis of DCIS until all atypical features are fully fledged. Some lesions called DCIS with other criteria are AH in the Page and Rogers system. Similarly, many lesions called AH in series with high incidences of this category would be diagnosed as PDWA using the Page and Rogers criteria. These two factors largely account for the lower RR for AH in the McDivitt et al. (32) and Carter et al. (29) studies in Table 1. Comparison of the Carter et al. (29) and Dupont et al. (31) studies is particularly instructive. Each dealt with the same cohort, the National Breast Cancer Detection Demonstration Project, but in Carter et al. the Page and Rogers criteria were not used and the pathology was not centrally reviewed. The risk stratification between PDWA and AH in Carter et al. was only 1.6-fold (3.0/1.9), while that in Dupont et al. was 3.3-fold (4.3/1.3). Other recent studies that do not have central pathology review (34) or fully adhere to the Page and Rogers criteria (34,35) have weaker stratifications similar to that in Carter et al.

The numbers of patients in the benign biopsy categories as well as the numbers developing breast cancers vary widely among studies, but the 95% confidence intervals in Table 1 provide a common, useful measure of the statistical power of the individual studies.

RR and Age

Table 1 shows the recent studies that have looked at age or family history or both as breast cancer risk factors in women with proliferative disease of the breast. In those that looked at age as a variable, younger women were at increased RR of breast cancer compared with the population at large. London et al. (30) found an accentuation of RR in younger women with AH (5.9 compared with 3.7 for older women), but not with PDWA on biopsy. From the National Institutes of Health-American Cancer Society Breast Cancer Detection Demonstration Project (BCDDP), Carter et al. (29) found increased RR for both PDWA and AH. They commented that the higher risks for AH may, among other reasons, "be the result of a preponderance of familial breast cancer among younger women" (29). In their study of the BCDP data, but with central pathology review, Dupont et al. (31) confirmed an increased RR for younger women, but showed that it was confined to the AH group (Table 1). While the formal statistics indicate an increased RR of breast cancer in younger women with AH, concern should be tempered by the fact that breast cancer rates are much lower in this age group.

RR and Family History

Most recent studies (*see* Table 1) show that the RR of breast cancer in women with proliferative disease is further increased by a positive family history. McDivitt et al. (32) did not observe this effect, but the number of patients with a positive family history was small, yielding unstable RR values and large confidence intervals. The studies that have central pathology review and that most closely adhere to the current consensus definitions

of PDWA and AH (17,18,20,21) show that the greatest amplification of RR with positive family history is confined to AH (17,18,30,31). In HBC and FBC families, a biopsy of AH is of sufficient concern to us to warrant the option of prophylactic mastectomy among management strategies (4,36).

Pathology of Early-Onset Breast Cancer

Studies of the pathology of breast cancer in younger women have been rather sparse, and many suffer from small size and lack of formal statistical significance testing of suspected trends. In this section, we review the literature and, in some instances, do hypothesis testing on the original data retrospectively, using chi-square or Fisher's exact tests on contingency tables, which may be somewhat limiting on our ability to draw conclusions. The *P* values (both original and retrospective) are provided to allow the reader to assess relative strengths of trends.

Table 2 shows the more notable studies on early-onset breast cancer pathology, some of which were cited in an earlier review (37). Some that are particularly informative report from geographic regions where early-age onset breast cancers make up a relatively large proportion of all cases [(38,39); reviewed in (37)]. In addition to the histopathology, we will also review DNA ploidy and tumor proliferative characteristics in younger women. From the literature and from some data that we present here, a number of distinguishing features emerge.

Increased Incidence of Medullary Carcinoma

The original report of Moore and Foote (40) essentially defined the medullary carcinoma as we know it today. The tumor is solid, well circumscribed, and often large, with broad anastomosing cell masses separated by stroma containing lymphocytes and plasma cells (Fig. 4). The most unusual attribute is its excellent prognosis in the pure form compared with ordinary infiltrating breast carcinomas, despite the anaplastic appearance of its cells (40,41). Medullary carcinoma "variants" also have been described. These have a prognosis closer to that of infiltrating duct carcinomas (41). The reported incidence of medullary carcinoma in first-world countries ranges from 2% to 10% (42).

While medullary carcinoma is a well-recognized type of breast cancer (40,41,43), the diagnosis is not straightforward, and in some reports [e.g., (44)], diagnostic concurrence among pathologists is imperfect. Studies on this histologic subtype should be viewed with this proviso.

In most reports, this unusual subtype of invasive breast carcinoma is more common in younger women. In the original study, 60% of patients were under age 50 (40). With one exception (45), similar disproportionately high incidences in younger patients or significantly earlier ages of onset have been noted in subsequent studies (Table 2) (33,34,46-51).

The increasing rate of medullary carcinoma with decreasing age in the Cancer and Steroid Hormone Study (CASH) (51) is illustrated in Fig 5. The incidence is plotted relative to infiltrating ductal, or "no special type (NST)," carcinoma, which is the most common type of breast cancer at all ages (76% in the CASH study), and remains fairly constant as a proportion of cases through the four age groups in the CASH study. The medullary/NST ratio plotted in Fig. 5 for different age groups is

Table 2. Early-onset breast cancer pathology: Literature review

Year	Investigators (ref. No.)	Remarks
1949	Moore and Foote (40)	52 of 1000 consecutive breast cancers were medullary; 60% of patients with medullary carcinoma are age <50
1968	Amaku (38)	Of 40 cases of breast cancer in Lagos, 17 (42.5%) were age <40. 8 of 31 cases (26%) were medullary type
1969	Schwartz (46)	Almost 50% of "solid circumscribed" (equivalent to medullary) carcinoma occurred before age 45, compared with 28% of breast cancers in general
1970	Brightmore et al. (57)	In patients under 35, a higher incidence of high-grade carcinomas (2 and 3)
1972	Rouessé et al. (59)	In women under 30, glandular differentiation was less common (2% vs 9%), medullary carcinoma more common (6% vs 1%), and there were more Scarff and Bloom grade 3 tumors
1975	Gogas and Skalkas (47)	Apparently large (22% of 162) incidence of medullary carcinoma in women <40, but no comparison group supplied
1975	Fisher et al. (48)	In young patients (aged 20-44) in a large series, there was more medullary carcinoma, more high-grade carcinomas, and more cellular reaction
1977	Vakil (53)	Intraductal and papillary carcinomas were more common in premenopausal patients (statistical significance not provided)
1980	Erdrich et al. (49)	In a large series of breast cancers (n = 2321), LCIS ($P < .0001$),* DCIS ($P < .01$),* and medullary carcinomas ($P < .005$)* were significantly more common in younger (≤ 54) women; pathology not centrally reviewed
1982	LiVolsi et al. (56)	Trend approaching significance ($P = .06$)* for increased ratio of invasive lobular to invasive ductal carcinoma in order (60-74) compared with younger (45-59) women
1985	Jacquemier et al. (54)	A greater incidence of invasive ductal carcinoma with a predominantly intraductal component in women less than 35 ($P = .009$),* and higher grade in invasive carcinomas in women less than 40 ($P = .04$)*
1987	Backhouse et al. (45)	No significant differences in breast cancer types in 59 patients younger than 35 compared with 264 consecutive breast cancers of all ages
1989	Stalsberg et al. (39)	In a WHO series of 2728 breast cancers and an age cutoff of 44, there was increased medullary and decreased lobular carcinoma in the younger patients ($P < .05$)
1993	Claus et al. (51)	More medullary carcinoma and DCIS, and less LCIS, invasive lobular, tubular, and mucinous carcinomas in younger women; by chi-square, only medullary trend was significant ($P < .0005$)*
1993	Marcus et al.	Increased DCIS in any form, with or without invasive component, in women ≤ 50 (this article)

* P values computed retrospectively from original published data.

derived from the percentage data presented in Table 2 of Claus et al. (51), which we transformed to actual case numbers. It is normalized to the medullary/NST ratio for all age groups combined. Our chi-square test of the differences in case numbers of medullary versus NST tumors in the 20-29, 30-39, 40-49, and 50-54-year-old age groups indicates a highly significant excess of medullary carcinoma in the younger ages ($P < .005$).

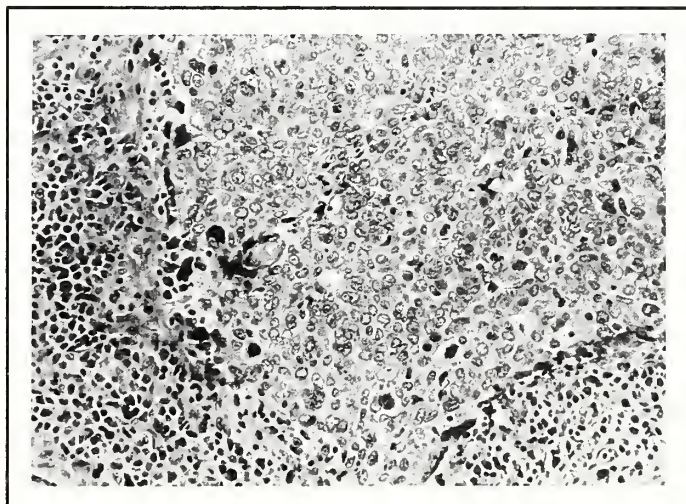


Fig. 4. Medullary carcinoma of the breast. Broad anastomosing nests of anaplastic tumor cells are invested by a lymphocyte-laden stroma (hematoxylin-eosin, $\times 200$).

Increased Incidence of DCIS

DCIS features atypical to anaplastic cells that are confined to the ducts and lobules, often distending them (52). The cells do not invade through the basement membrane into the stroma, hence the term "in situ." Two major types are recognized, comedo and non-comedo, the former having a greater association with invasive carcinoma. In most of the literature on DCIS in younger ages, distinction is not made between subtypes.

Most studies appear to show a trend toward increased incidence of DCIS in younger patients (Table 2). However, assessment of pure DCIS alone is made difficult by its low frequency, differing sensitivities in its detection and lack of central pathology review. As shown in Table 2 (with our retrospective computations of P values), some studies show excess DCIS of indeterminate (53), some (49), or no (51) statistical significance in younger ages, while others show no trends (39,45).

Invasive carcinomas often are accompanied by an intraductal component. When this component predominates ($>80\%$), the cancer is classified as "invasive ductal carcinoma with a predominant intraductal component" (IDCPIC) (43). An excess of IDCPIC in younger women was found in breast cancer cases at Marseilles by Jacquemier et al. (54). From their Table 1, IDCPIC was commonest in the youngest (under 35 years) ages, where they were 57% of the cancers (by chi-square our computation yields $P < .01$). In the World Health Organization (WHO) study of 2728 breast cancer patients by Stalsberg et al. (39), women older than 44 had only 70% of the incidence of

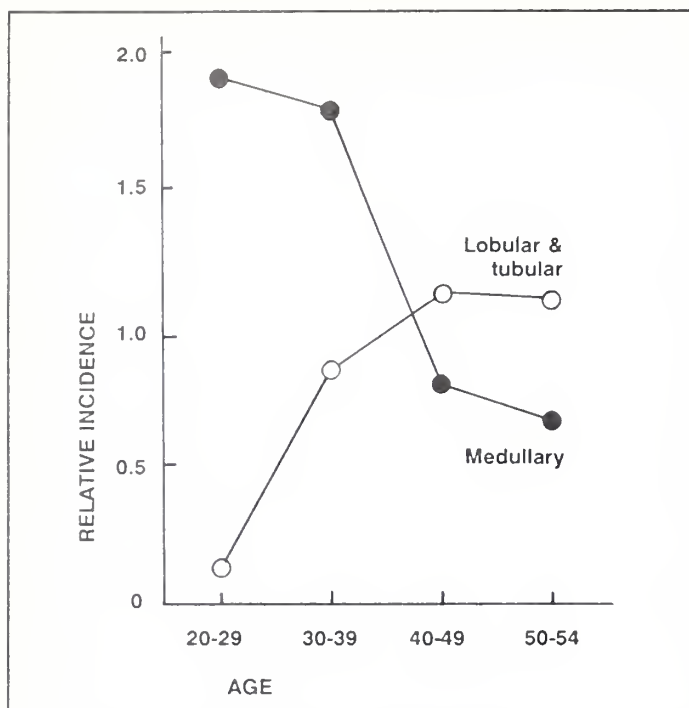


Fig. 5. The incidence of medullary carcinoma and of tubular and lobular carcinoma, relative to that of infiltrating ductal (NST) carcinoma as a function of age. Derived from data in Table 2 of Claus et al. (51)

IDCPIC relative to women 44 or younger. The excess of IDCPIC in the younger women, however, was not statistically significant. The incidences of IDCPIC were very different in the two studies.

We looked for DCIS in any form in a consecutive series of 187 breast carcinomas accessioned at first diagnosis by the Tumor Registry of St. Joseph Hospital in Omaha. The diagnoses included DCIS in any amount accompanying invasive carcinomas, as well as pure DCIS. In women under age 50, 18 of 37 (49%) had any form of DCIS compared with 42 of 150 (28%) in women 50 years of age or older ($P < .02$). There was no significance difference in pure DCIS incidence, however.

Lobular Carcinoma In Situ

LCIS is a noninvasive epithelial cell proliferation located mainly in the lobules, although it also can be found in terminal ducts (just as DCIS can ramify into lobules). It is composed of small monotonous evenly spaced cells with bland nuclei and frequent cytoplasmic vacuoles. LCIS is often multifocal and is a biopsy-risk marker for concurrent or subsequent invasive carcinoma in both breasts, with a 15%-20% occurrence ipsilaterally and a 10%-15% occurrence contralaterally to the biopsy site after 15 years' follow-up (52).

Data on relative incidence of LCIS in younger women are conflicting. In their series, Rosen et al. (50) noted an average age at presentation of 53 years, compared with 58 years for DCIS, but they did not do statistical significance testing. Their conclusion was that "most if not all LCIS develops in patients at a younger average age than does duct carcinoma." From data reconstructed from Table 1 of Erdreich et al. (49), we found a significant association between age group and LCIS relative to

invasive NST by chi-square test ($P < .001$): women less than 55 years old had the highest rates (3.3%) compared with older women (0.8%). On the other hand, from the data derived from Table 2 of Claus et al. (51), we find a near-significant trend for more LCIS in older ages (chi-square: $P = .07$).

Decreased Relative Incidence of Invasive Lobular and Tubular Carcinoma

Invasive lobular is a "special type" carcinoma composed of generally small cells, often with small vacuoles, which tend to infiltrate in a single-file fashion. All subtypes appear to be associated with an increased risk for contralateral invasive breast cancer, and the classic form has a somewhat better prognosis than invasive NST (55). Tubular carcinoma, as the name implies, is composed almost exclusively of well-differentiated tubules. The nuclei are bland and usually small. The tumor is usually small and is associated with an excellent prognosis. A special type carcinoma with hybrid qualities of invasive lobular and tubular carcinoma, tubulolobular carcinoma, has been recognized (55). Its prognosis is intermediate between pure tubular and NST invasive carcinomas.

Studies show a trend for a lower relative incidence of invasive lobular carcinoma in younger women. In a case-control study, LiVolsi et al. (56) looked at the relative incidences of invasive ductal and lobular carcinomas as a function of hormonal risk factors and age in 332 women aged 45-74. From the original data in Table 1 of LiVolsi et al. (56), the invasive lobular/NST ratio was 7.3% in women less than age 60 compared with 15.7% for women 60 or older. Our computation shows that the trend for less invasive lobular carcinoma in the younger age group approaches statistical significance ($P = .06$). Nulliparity and late age of first birth were associated with a higher risk of NST carcinoma and a lower risk of invasive lobular.

Stalsberg et al. (39) found a higher risk of invasive lobular carcinoma in women over 44 years of age in the WHO series compared with women 44 years old and younger ($RR = 1.3$; $P < .05$). The RR for tubular carcinoma in this age group was the same, but the increase was not statistically significant. The proportion of tubular and lobular carcinomas considered together peaked in the 45-49 age group. Compared with age 39 or younger, the odds ratios for the combined incidence in the 40-49 and 50 or greater age groups were 1.73 and 1.28, respectively ($P < .001$). There was an associated significantly increased odds ratio for lobular or tubular carcinomas in countries with higher risks of breast cancer and in women with a prior benign breast biopsy, bilateral breast cancer, concurrent mammary "dysplasia," and later age at first live birth. The authors speculated that the cell of origin for lobular and tubular carcinomas was different from that for breast cancers not associated with these risk factors.

From the data in Table 2 of Claus et al. (51), a deficit of tubular and lobular carcinomas can be demonstrated in the younger cases, an effect most prominent in the 20-29-year-old age group. By our chi-square analysis of the percentage data transformed to case numbers, age group differences are significant ($P = .02$). The normalized odds ratio of tubular or lobular carcinoma relative to NST carcinoma is plotted in Fig. 5.

Higher Grade

A number of grading systems for invasive breast carcinoma exist, and in most, ascending grade correlates to shorter survival. Brightmore et al. (57) found that in breast carcinomas in women under 35 years of age, there was a higher fraction of grades 2 and 3 in comparison to an earlier series (58) that included all ages. Similarly Rouessé et al. (59) reported an increased incidence of high-grade carcinomas in women under 30, as did Fisher et al. (48) in women under age 44 (Table 2). In the Marseille series (54), nine of 16 (56%) carcinomas in women less than age 40 were high grade (grade 3) compared with 36 of 124 (29%) in women older than 40 (Table 2). By our Fisher's exact test the difference is marginally significant ($P = .04$).

Lesser or Equal Incidences of Aneuploidy

Cancer cells usually have a discrete modal DNA content that most broadly can be classified as diploid (DNA content of G_0G_1 cells indistinguishable from that of normal cells) or aneuploid (content different from normal cells). Ploidy in breast cancers has been most widely studied by DNA flow cytometry for tumor DNA content. Most breast cancers are aneuploid (64%), with frequencies ranging from 44% to 92% in a recent review of 15 studies (60). Aneuploidy generally has been associated with poorer prognosis, although ploidy may not be independent of other clinicopathologic prognostic parameters (60).

Most studies show an equal or a lower incidence of aneuploid breast cancers in younger or premenopausal women compared with older women (60). In studies subsequent to 1988, a decreased incidence of aneuploidy in women younger than 50 was reported in a series of 141 patients by Joensuu et al. (61) ($P = .05$), and in premenopausal women in a series of 122 patients studied by Eskelinen et al. (62) ($P = .03$ by our computation). Our data (Table 3) suggest a decreased aneuploidy rate in women younger than 50 (14/27 = 52%) compared with those 50 or older (67%), but the difference is not significant ($P = .18$). Beerman et al. (63) found no differences in ploidy distribution between women younger and older than age 50 in 690 breast cancers that they evaluated.

Higher Proliferation Rates

The proliferation rate of tumor cells can be assessed in a number of different ways. The classical studies utilized uptake of tritiated thymidine by cells in the synthetic (or S) phase of the cell cycle. These tumor cells are counted by autoradiography

and a thymidine-labeling index (TLI) is derived. Tumors with high TLIs are associated with shorter relapse-free intervals and survival intervals (60), independent of stage (64).

TLI is higher in breast cancers from younger women (64-67) as illustrated in Fig 6. There is also an inverse relationship between TLI and age and TLI and estrogen and progesterone-receptor content (64-66).

These same relationships are also generally observed when cellular proliferation is measured as DNA S-phase fraction (SPF) by flow cytometry, including recurrence rates and survival times (53,68,69). Inverse correlation of SPF to age has been noted in most (60,68,70,71) but not all (72) series. SPF also is inversely correlated to hormone-receptor content in most studies (60). In their series of 1184 frozen breast tumors, Dressler et al. (70) found significantly higher SPFs in premenopausal women in both diploid and aneuploid cancers. Aneuploid breast cancers in most studies have much higher SPFs than diploid breast cancers (60,62,70,72), as is evident in our data from St. Joseph Hospital (Table 3). Our data also indicate that SPF is higher in younger women, an effect confined to the aneuploid cancers (Table 3).

Ki-67 is an example of an antibody against a proliferation-associated protein that can be used to immunohistochemically label the nuclei of proliferating cells. The number of cells positive for Ki-67 in breast cancers has been reported to be higher in younger (73) or premenopausal (74,75) women.

Whether measured by thymidine labeling, DNA flow cytometry, or proliferation protein recognized by antibody Ki-67, breast tumor cell proliferative rates are higher in younger women.

Pathology of Familial and Hereditary Breast Cancer

The association between histologic subtypes of breast cancer and family history of breast cancer has been the subject of a number of brief reviews (4,39,51,76). The oldest, that of Mul-

Table 3. Age and S-phase fraction (SPF)

Age, y	No. of cases	SPF (mean \pm SD)*	P†
<i>Diploid</i>			
<50	13	2.71 \pm 1.74	NS
\geq 50	39	3.08 \pm 2.01	
<i>Aneuploid</i>			
<50	14	12.18 \pm 6.57	<.04
\geq 50	79	8.81 \pm 4.71	

*SPF = S-phase fraction; SD = standard deviation.
†P value from standardized U test; NS = not significant.

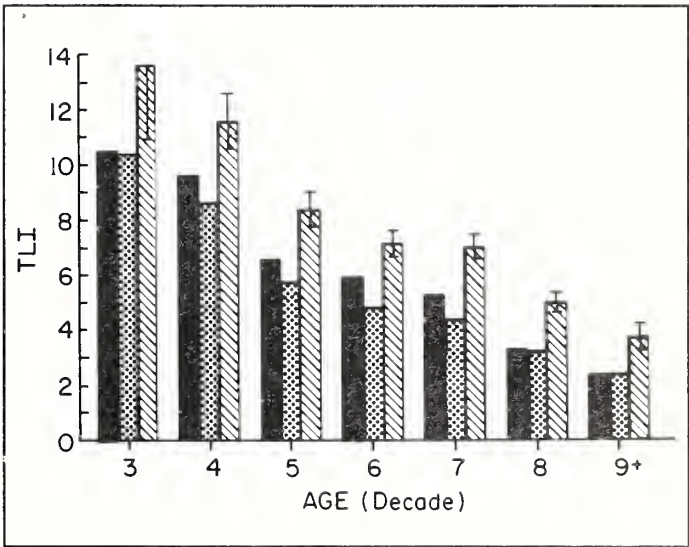


Fig. 6. Thymidine-labeling index, a measure of tumor proliferation, is higher in younger patients with breast cancer. The solid, shaded, and hatched bars are median, geometric mean, and mean, respectively. Error bars = standard error of the mean. Modified from Meyer et al. (64), with permission of author and U.S. Canadian Academy of Pathology, Inc.

cahy and Platt (37), is also the most comprehensive: in addition to family history, relationships of pathology to early-onset disease, bilaterality, and geographic and ethnic variables are reviewed. Most of the studies concern *familial* breast cancer as earlier defined, while data on *hereditary* breast cancer pathology are beginning to be assembled.

As with the literature on breast cancer pathology in younger women, many studies suffer from small size and lack of a formal statistical approach. For this reason, retrospective significance testing will be done here as needed, as in the previous section. While trends for an association of certain histopathologies with family history do emerge, it is fair to say that they are not strong, so that tumor histopathology and positive family history are not particularly strong predictors of one another.

Table 4 summarizes the literature on the association of histopathologic type and family history of breast cancer. The discussion below will be divided between familial and hereditary breast cancer as earlier defined.

Familial Breast Cancer

Ductal carcinoma in situ. Despite its increased prevalence in younger ages (previous section), most studies do not report a correlation of this histopathologic type with a positive family history. Of those that do, Anderson's result (2) is paradoxical, yielding a deficit of DCIS in mothers of women with breast cancer ($P < .05$), but an excess in sisters (P value not provided). Erdreich et al. (49) reported an increase in both papillary and comedo DCIS in women with first- or second-degree relatives with breast cancer. However, the numbers in the study were

quite small, and when both these types are combined, we compute no statistical significance by Fisher's exact test ($P = .15$).

Lobular carcinoma in situ. Studies of LCIS are conflicting. The association of this histologic type with a positive family history can be traced to a report by Haagensen (77) that 14% (seven) of 53 patients with LCIS (called "lobular neoplasia") had mothers with breast carcinoma, higher even than that in mothers of breast carcinoma patients (9%). No actual comparison patient numbers were provided, but it is unlikely that this apparent difference is of any statistical significance. Rosen et al. (78) reported that there is an increased frequency of sisters with breast cancer among women with LCIS (and a decreased frequency of breast cancer in sisters of women with medullary carcinoma). Claus et al. (51) find that 23% of women with LCIS report a mother or sister with breast cancer, approximately twice that for any other histologic subgroup. No formal statistical significances were provided for this odds ratio. However, on transforming the percentage data of their Table 2 to case numbers, we compute the excess of LCIS in families relative to invasive NST carcinoma to be significant by chi-square ($P = .002$). Their LCIS cases were also more likely to be bilateral. On the other hand, from Table 5 of Erdreich et al. (49), there is a deficit of LCIS in patients reporting a family history (first and second degree) of breast cancer: none of 31 patients with LCIS had a family history, compared with 76 of 643 for all histologic types. This negative trend approaches statistical significance in our computation (Table 4). Other studies (2,37) report no association of family history and LCIS.

Table 4. Familial and hereditary breast cancer: literature review

Year	Investigators (ref. No.)	Remarks
1972	Haagensen (77)	14% of 53 patients with LCIS had mothers with breast cancer, compared with 9% of patients with "carcinoma of the breast"
1974	Anderson (2)	Higher incidence of medullary carcinoma ($P < .02$) and DCIS ($P = ?$) in pedigrees with sisters with breast cancer; mother pedigrees showed no increase in medullary and a decrease in DCIS
1977	Vakil et al. (53)	A higher proportion of patients having lobular carcinoma and "adenocarcinoma" "had familial breast cancer" (not defined); no statistics provided
1980	Erdreich et al. (49)	Nonsignificant trends for association of DCIS ($P = .15$),* invasive lobular ($P = .17$)* with positive family history and LCIS ($P = .07$)* with negative family history (1st- and 2nd-degree relatives)
1980	Lagios et al. (80)	Trend for positive family history in 6 of 15 patients with tubular carcinoma, compared with 31 of 194 with other carcinomas, approaches significance ($P = .08$)*
1981	Mulcahy and Platt (37)	Marginally significant trend for increased medullary carcinoma in familial breast cancer compared with sporadic breast cancers (12 of 75 vs. 2 of 54; $P = .04$)*
1982	Rosen et al. (78)	Maternal breast cancer significantly ($P < .006$) more frequent among women with medullary carcinoma; sororal breast cancer more frequent among women with LCIS and least frequent with medullary ($P < .03$)
1982	LiVolsi et al. (56)	A nonsignificant ($P = .30$)* association of lobular carcinoma and a history of breast cancer in a mother or sister
1984	Birch et al. (82)	Of mothers of 143 children with soft tissue sarcomas, 6 had breast cancer (2 were bilateral), a 3-fold excess; 4 of 8 tumors were lobular, tubular, or tubulolobular, and another had lobular features
1988	Marcus et al. (83)	High mitotic grade in invasive NST hereditary breast cancers compared with sporadic breast cancers
1989	Stalsberg et al. (39)	No significant increase of tubular or lobular carcinoma in patients with a positive family history ($.05 < P < .10$)
1990	Mosimann et al. (81)	Nonsignificant trend ($P = .18$)* for positive family history in tubular compared with invasive ductal carcinoma
1990	Bürki et al. (79)	No difference in relative incidence of breast cancer in 1st-degree relatives of patients with medullary, tubular, or infiltrating ductal carcinomas
1993	Claus et al. (51)	Increased RR of breast cancer in mothers or sisters of patients with lobular carcinoma in situ
1993	Marcus et al. (84)	High DNA flow cytometry S-phase fraction in hereditary breast cancer

* P values computed retrospectively from original published data

Medullary carcinoma. Anderson (2) first reported an association of this histologic subtype with positive family history of breast cancer. Patients who had sisters with breast cancer were significantly more likely to have medullary type (Table 4). However, those who had mothers with breast cancer showed no significant increase of medullary type. In contrast, Rosen et al. (78) reported increased medullary carcinoma in patients with mothers with breast cancer ($P < .006$), but a decrease in women with sisters with breast cancer ($P < .03$; Table 4). Other studies (39,49,51,79) find no association of family history and medullary carcinoma. In a large series of patients with medullary carcinoma, increased bilateral cancer (medullary and nonmedullary) has been associated with a family history (41).

Tubular and lobular carcinoma. Studies are hindered by small numbers of patients and low frequencies of these two histologic types. Vakil (53) stated that a higher proportion of patients with lobular carcinoma had a positive breast cancer family history but provided no numbers. Rosen et al. (78) found a sororal association of lobular carcinoma, apparently both invasive and LCIS, and positive family history in comparison with medullary carcinoma. In cases with histories of maternal or sororal breast cancer studied by LiVolsi et al. (56), there was a higher incidence of invasive lobular carcinoma. From percentage data in their Table 2 transformed to case numbers, seven of 32 lobular carcinomas, compared with 41 of 284 ductal carcinomas, had a positive family history. We compute that this trend is insignificant ($P = .30$). Stalsberg et al. (39) reported an increased family history in invasive lobular carcinoma that approached statistical significance (Table 4). On the other hand, Claus et al. (51) found no association, and a decreased incidence of invasive lobular carcinoma with a positive family history approaching statistical significance was found by Erdreich et al. (49) (Table 4). Overall, results on a positive association of lobular carcinoma and family history are suggestive, but inconclusive. Tubular carcinoma is reported by Lagios et al. (80) to be associated with an increased risk of breast cancer in mothers, sisters, and maternal aunts. Six of 15 patients (40%) with tubular type, compared with 16% of the remaining types in the series, had a family history. Our retrospective computation shows that this trend approaches significance by Fisher's exact test ($P = .08$). Mosimann et al. (81) looked at incidence of tubular carcinoma in first-degree relatives and found a higher rate (10/37 = 27%) than in invasive NST carcinoma (18%). Our computation by Fisher's exact test shows that this trend is not significant ($P = .18$). A threefold excess of breast cancer has been reported in the mothers of 143 children with soft tissue sarcomas (82). Half of the cancers were tubular, lobular, or tubulolobular, which is in excess of the expected frequencies for these relatively rare types (Table 4).

Hereditary Breast Cancer

The pathology of hereditary breast cancer is of increasing importance now that a major breast cancer gene, BRCA1, has been localized (6-8). This major gene will better define inherited cancers that had earlier relied exclusively on pedigree and clinical data.

There have been only a few studies of HBC pathology. Using the pedigree-defined HBC resource at Creighton University,

Mulcahy and Platt (37) reported a collective excess of medullary carcinoma: 12 of 75 HBC cases, compared with only two of 54 sporadic breast cancers, were medullary type. Our retrospective computation by Fisher's exact test indicates that this excess is significant ($P = .04$). Marcus et al. (83) confirmed this result ($P < .05$) in the updated and extended series of Creighton families with breast cancer. However, medullary carcinomas occur more frequently in younger ages (previous section). When adjusted for the age covariate, the medullary excess in HBC loses statistical significance.

Marcus et al. (83) also showed that there is a higher mitotic grade in invasive NST carcinomas in HBC compared with sporadic breast cancers. Twenty-two of 35 HBCs were mitotic grade 2 or 3 compared with 11 of 33 of the controls ($P < .02$). This result is important because invasive NST carcinomas comprise the bulk of breast cancers (about 75%), while medullary and other special type invasive carcinomas are comparatively uncommon. The result holds in our current much enlarged data set and is independent of patient age (Marcus JN, et al.; manuscript in preparation). Preliminary DNA flow cytometric data from our resource also suggest that HBC has a higher proliferation rate, as measured by S-phase fraction, than non-HBC, a result likewise independent of age (84). There is also some suggestion that the HBC subset linked to the q12-21 region of chromosome 17 has higher SPFs.

Discussion and Future Directions

Because of the high incidence of hereditary breast cancer (and "positive family history") in early-age onset breast cancer, we have reviewed the premalignant and malignant breast pathology in younger women from the dual perspectives of early-age onset pathology per se, and the pathology of familial associations. This approach is informative, as reinforcing parallels emerge. As examples, in the AHs, the increased RR for breast cancer is further amplified both in the younger age groups and in young women with positive family histories of breast cancer. In both instances, although there is a minor further increase in RR for biopsies with PDWA, the main amplification occurs with AH. In the pathology of the tumors, a trend for increased medullary carcinoma and higher grade NST cancers is seen both in younger women and in familial and hereditary breast cancer. Likewise, tumor cell proliferation is higher in younger women and in HBC patients.

These observations suggest that the target cell for carcinogenesis in the breasts of women who develop breast cancer early, and/or who are genetically predisposed to breast cancer, may be "on a fast track" for malignant transformation. In current paradigms of carcinogenesis, the target cell is seen as a proliferating stem cell. Increased proliferation of normal and intermediate cells itself can be regarded as "carcinogenic," increasing the chances for deleterious mutations, malignant transformation, and tumor progression (85-88). The association of atypical hyperplasias in the breast with increased RR of carcinoma is compatible with this view, in a manner parallel to the association of the proliferative APC gene mutation with the development of colon carcinoma in *familial adenomatous polyposis* (89,90). Such proliferation mutations as occur in

familial adenomatous polyposis have aptly been termed "promotor" mutations (89). Whether the BRCA1 gene that accounts for much of the hereditary breast cancer burden is such a proliferation or promotor mutation remains to be proven, but current models view its action as early in the sequence that leads to malignant transformation (91).

A tumor that is more genetically evolved has accumulated more chromosomal defects and, in the case of breast cancer, has been shown to have a higher DNA flow cytometric SPF (71). Breast cancers in both younger women and in hereditary pedigrees (in our preliminary data) also have higher SPFs than those in older women or in nonhereditary tumors. This would suggest that such tumors are more genetically evolved, and leads to an hypothesis that the advanced evolution may be due to a mutation for enhanced proliferation. Thus, the pathology of early-age onset or hereditary breast cancer might shed light on the nature and function of the BRCA1 gene, once it is precisely located, cloned, and sequenced. An understanding of the nature of this gene in turn may lead to new methods of treatment of cancers or prophylaxis in individuals at risk for breast cancer before it develops.

IDCPIC appears to be increased in frequency in younger women (54). It has also been observed that women with invasive carcinomas with extensive intraductal components have higher rates of recurrence after conservation therapy (92-95). Whether more extensive IDCPIC in younger women accounts for the apparently higher recurrence rate in this age group is an issue that needs further study. Other factors, such as higher tumor proliferation rates, could also be responsible.

The higher SPF in the invasive breast cancers of younger women has practical implications, for high SPF tumors are associated with earlier recurrences and decreased survival times (60,64). The higher tumor proliferation rates, however, may also be a source of hope for better-targeted therapeutic intervention. One recent study (96) shows that breast cancers with higher SPFs are the ones that are most likely to respond to adjuvant chemotherapy.

Thymidine-labeling studies (97,98) have demonstrated that the proliferation of terminal ductal-lobular unit cells in younger women is higher than in older women. This is of particular interest in the context of the proliferation paradigms of carcinogenesis, for it suggests that immediately postpubescent breasts should be at higher risk of accumulating mutations that may lead later to cancer. Evidence from various sources indicates that this may indeed be the case: 1) Early first pregnancy, which induces differentiation of the breast and may remove cells from the proliferative compartment (98), is associated with a decreased breast cancer risk (99). 2) Very early oral contraceptive use in some (100-102), but not all (103), studies is associated with a significantly but usually small increased risk of subsequent breast cancer. 3) Women survivors exposed to radiation from the Hiroshima and Nagasaki atomic bombs manifest an increased incidence of later breast cancer that is particularly marked in those aged 10-19 years at the time of the blasts (104,105). 4) In rats, the efficiency of carcinogen-induced breast cancer is maximal in the immediate postadolescent period (106,107), when cell proliferation rate is highest. These observations provide a rationale for hormonal modulation strategies to

put breasts of young women more "at rest" in the period between menarche and first birth in an attempt to prevent breast cancer (108,109).

This review demonstrates some differences in pathologic and proliferative characteristics of breast cancers in younger women and in women with positive family histories, as well as in breast cancer risk associated with AH. A combined approach of classical, genetic, and molecular pathology will be key in understanding, treating, and preventing breast cancer in younger women. The major task at hand is the isolation and characterization of the BRCA1 and any other genes that are involved in the pathogenesis of breast cancer, particularly in young women. This new knowledge should lead to more directed prevention and treatment strategies.

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Breast Cancer Outcome and Predictors of Outcome: Are There Age Differentials?

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Several questions were addressed regarding breast cancer outcome, predictors of outcome, and young age at diagnosis. Is there evidence that outcome is worse in younger women compared with other age groups? Do younger patients have a greater frequency of adverse prognostic factors? If younger age is associated with a poor outcome, is it an intrinsic independent adverse predictor, or is the outcome worse due to poor prognostic factor profiles? Several methods were used to answer these questions and applied to those reports in which age categories were carefully defined: 1) detailed review of population-based breast cancer outcome literature, 2) synthesis of published cooperative group and single institution univariate and multivariate analyses, and 3) a new analysis of the 8738-patient San Antonio database. Overall, epidemiologic studies suggested that younger women have the worst survival outcome, when matched with similarly staged older cohorts. Univariate trends analyses confirmed that younger women more often had more positive lymph nodes, larger tumors, and negative steroid hormone receptors. Significantly more cancers in women less than 35 years of age had high S-phase fractions and abnormal expression of p53. Multivariate modeling confirmed that young age was an independent adverse predictor when a few standard factors were considered in the model, but other descriptors such as tumor grade or high S-phase fraction were more important when available. These data support the conclusion that "young age" serves as a surrogate for a greater frequency of adverse prognostic factor profiles and suggest important questions for future study. [Monogr Natl Cancer Inst 16:35-42, 1994]

There are several questions regarding breast cancer outcome and younger age that are important to consider. First, is breast cancer outcome (disease-free survival [DFS]; overall survival [OS]) worse in younger women compared with older premenopausal and/or with postmenopausal women? Second, are there age trends in univariate predictors of outcome (younger patients have more of the adverse prognostic factors)? Third, if younger age at diagnosis is indeed associated with a poor outcome, is it an intrinsic independent adverse predictor of DFS and OS, or is outcome worse in younger women due to poor prognostic factor profiles? Fourth, are independent predictors of DFS or OS similar or different across various age groups?

A wide range of answers to some but not all of these questions are available (1-5). There are three types of reports: either

all-inclusive or limited population-based series (6-12), single institution retrospective analyses (13-21), or Cooperative Group databases (22-27). The statistical methodology applied in these reports is highly variable, in many cases without multivariate modeling. Furthermore, young age is not consistently defined. For example, either 30 years or less, 35 years or less, 40 years or less, 50 years or less, or "premenopausal" is variably used to define the youngest subset.

Therefore, the objective of this investigation is to provide answers to the four questions posed above. Two approaches will be used: 1) a review of the published series regarding breast cancer outcome, predictors of outcome, and accompanying age trends with respect to each of the four questions, and 2) a new analysis of the large San Antonio early breast cancer database, with a specific focus on prognostic factors, age trends, and multivariate models.

Methods

Review of Published Data

Population-based series that offer conclusions regarding breast cancer outcome (DFS and/or OS) in younger age groups were identified and reviewed. Our investigation was limited to reports that specify age categories *within* the subset of women either under 50 or "premenopausal." The series were also analyzed to determine whether stated conclusions regarding different outcome by age were justified by the use of controls for stage of disease or other potential prognostic factors. In addition, reports were assessed to determine if the younger age group was compared with stage-matched patients in other age groups, if treatment was specified, and if outcome was adjusted for expected mortality and noncancer deaths.

A large number of reports identified an adverse outcome in younger women and then related this to an unfavorable distribution of a single prognostic factor (*univariate* analysis). Certain reports were selected for review, which not only specified prog-

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See "Notes" section following "References."

nostic variables and univariate trends by age subsets, but also analyzed all factors together to rule out interactions (*multivariate* methods). Thus, the independent contribution of younger age to adverse outcome was tested. These data were only available in referral populations such as single institution or cooperative group databases. In addition, univariate and multivariate results from a new San Antonio database analysis (*see* next subsection) were provided and discussed in context of the results of these other series.

Finally, a survey of the literature plus the new San Antonio analysis (*below*) addressed the question of whether predictors of outcome differ for younger women, or whether the same prognostic factors independently predict outcome in younger and older subsets.

New Analysis of the San Antonio Database

The organization and characteristics of this early breast cancer database are reviewed in detail elsewhere (12). Frozen tumor specimens large enough for standard receptor assays were sent by community surgeons to the tumor bank at the University of Texas Health Science Center at San Antonio. Only primary, nonmetastatic cases were considered. Primary surgical treatment and adjuvant therapy, if given, were rendered by community physicians. Surgery and pathology reports, treatment records, and disease recurrence and death dates were obtained by experienced data managers. Tumor specimens were analyzed for a number of potential prognostic factors, including estrogen receptors (ER), progesterone receptors (PgR), and S-phase fraction and DNA ploidy determined by flow cytometry (28), expression of the HER-2/neu oncogene (29), cathepsin D (30), and the p53 tumor suppressor gene (12).

Previous analyses of this database used the standard $<$, \geq age 50 dichotomy and consistently found no independent contribution of age to prediction of DFS. Thus, for this investigation, "standard" prognostic factors (ER and PgR status; lymph node status, positive or negative and number positive; tumor size, T) and "new" potential factors (ploidy status, S-phase fraction, HER-2/neu, cathepsin D, and p53) were analyzed in univariate and multivariate analyses with age categories narrowly defined. The sample size of each univariate comparison was variable, based on the size of the specimen, as well as the type of factor and the year its analysis became feasible; $n = 8738$ for age and number of positive nodes; 8116 for age and tumor size; 8671 for age and ER; 7646 for age and PgR; 3012 for age and S-phase fraction; 3560 for age and DNA ploidy status; 758 for age and HER-2 expression; 384 for age and cathepsin D level; and 680 for age and p53 overexpression. The p53 data were available only in the node-negative subset; all other factors were a mixture of node-positive and node-negative cases.

Chi-square tests and Mantel-Haentzel tests for linear trends were used to compare the incidence of various factors across age groups. Univariate analyses of disease-free and overall survival were performed with the use of the Kaplan-Meier (31) method for dichotomized variables and Cox's (32) partially non-parametric regression model for continuous variables. Tests of differences between curves were made with the logrank test for censored survival data (33). Cox's model was also used to evaluate various combinations of prognostic factors in a multi-

variate manner. A variety of exploratory analyses were performed to identify the most appropriate representation of continuous factors. The square root transformation performed best for the number of positive nodes and tumor size, whereas a logarithmic transformation was optimal for S-phase fraction. In some analyses, patients were categorized into various age groups (<30 , 30-35, 35-40, 40-45, 45-50, and >50) using indicator variables to avoid the assumption of monotone hazard rates. Adjusted disease-free and overall survival rates were obtained by evaluating the Cox models for specific covariate patterns that corresponded to patients with median values of each of the relevant covariates. All statistical analyses were performed using SAS on a Sun Microsystems SparcStation.

Results

Literature Review, Population-Based Series

Two large population-based studies that employed narrow age categories suggested that the very young woman with breast cancer had an adverse outcome compared with other age groups. The Norwegian analysis described the worst OS in those patients under age 34 (adjusted for the normal population) (7). This poor outcome was not explained by an unfavorable mix of crudely defined stage categories. In the Swedish population, age under 30 was correlated with unfavorable OS; no analysis of correlation with distributions of stage or other potential prognostic factors by age category was provided (6). Neither of these reports gave details regarding adjuvant therapy, nor was stage-adjusted OS reported for the youngest age group versus others.

Several other population-based reports matched younger with older women on a stage-by-stage basis, but with conflicting results. The Charity Hospital series found no difference in outcome in stage subsets by age (14). There was no independent effect of young age in a multivariate analysis. In contrast, a Memorial Sloan-Kettering case-control analysis of 100 consecutive women under age 30 described a worse outcome for each stage subset, compared with the OS for stage-matched older patients (13). The American Cancer Society national survey reported that the 5-year OS was worse in the age subgroup under 35 for both the node-negative and node-positive populations (9). The frequency of the presence of axillary node metastases did not differ in the younger age groups compared with the older subsets. Other factors were not analyzed. The National Cancer Institute series reported an adverse 8-year OS outcome in both local and regional stage subsets for patients under age 35 (10). There was no difference in stage or histologic variable distributions among narrowly defined age categories. Several of the population-based reports and others (5-7,9) noted that although the very young patient did worse, older premenopausal or perimenopausal women had the best OS of any age group.

Two limited population-based series also concluded that young age was an adverse predictor, but only in certain stage subsets. The Christie/Holt Radium Institute investigators reported more women had advanced stages of disease in the group under age 30 (8). Outcome (OS) was significantly worse for the youngest women with stage II and stage III disease but not in the stage I subset. In the M. D. Anderson study (21), the node subsets of 0, 1-3, and ≥ 4 positive were examined. The 10-

year DFS was significantly worse for women under 30 in general, for those with large (T3) tumors who were under 30, and for those under 30 with negative nodes. No other nodal subset had a different outcome by age.

Literature Review, Younger Age and Prognostic Factor Profiles

A large number of retrospective reports assessed age with respect to a single prognostic factor to search for an explanation of the worse outcome in younger women. Overall, the studies suggested that younger women had a more adverse profile for the particular factor in question (e.g., advanced "stage," positive nodal status, more positive nodes, worse tumor grade, higher rate of proliferation, larger tumor size, negative ER/PgR status, and various adverse histologic variables). However, these conclusions were inconsistent, and the majority of these series either assessed only one factor or else did not correct for the inter-relationship of many of the factors in a multivariate analysis. Furthermore, there was no significant data regarding very young age and new adverse prognostic factors such as high S-phase fraction, aneuploidy, HER-2/neu overexpression, nm23 underexpression, elevated heat shock protein, high cathepsin D, epidermal growth factor receptor (EGFR) positivity, abnormal p53 expression, or elevated haptoglobin-related protein (34).

However, a few series carefully assessed distributions of standard prognostic factors within clearly defined age categories and subsequently analyzed for interactions with multivariate models (below). Two univariate analyses will be cited in detail. First, the Southwest Oncology Group (SWOG) node-positive database analyses reported DFS and OS outcomes with respect to younger age as one focus of the investigation (22). There were 768 patients entered on identical treatment arms of the first four SWOG phase III adjuvant trials. Available variables were age, number of positive nodes, menopausal status, breast cancer in mother, ER status, ER and PgR levels, race, tumor size, obesity index, and age at menopause. Various age cut points were examined, and three categories emerged (with different DFS and OS): under 35 and premenopausal (poor), 35 years or more and premenopausal (best), and postmenopausal (intermediate) (22). There was an excess of more than six positive nodes in women under age 35 compared to those in the other two categories (marginal significance), and no other variable was distributed differently among the three age groups. There was no evidence of different effects of age within node subsets for OS. However, in the ER-positive cohort, OS may have been worse in the youngest subset; there was similar OS by age category in the ER-negative subset (Green S: personal communication, 12/92).

The second univariate analysis of multiple factors within age categories was done in the south Sweden node-negative population (11). Three age groups were formed: 49 years or less, 50-74 years, and 75 years or more; no subsets within the youngest age group were analyzed, since only 11 patients were under 35. The DFS, but not the OS, was significantly worse in the youngest age group. There was a positive correlation of age with ER positivity ($P = .0005$), PgR positivity ($P = .03$), and aneuploidy ($P = .04$). Age was inversely related to higher S-phase fractions ($P = .0005$), but not larger tumor size.

New San Antonio Analysis, Univariate Results

A total of 8738 patients were available for these analyses. The median follow-up of patients still alive at the time of analysis was 47 months. Tests for linear trend for each factor were done across the age groups (<30, 30-35, 35-40, 40-45, and 45-50) for node-positive and node-negative cohorts together. There was a significantly greater number of the youngest women with more than three positive nodes, positive nodes in general, negative ER and PgR, larger tumors, and high S-phase fractions. The result for S-phase is shown in Fig. 1. Neither ploidy status, cathepsin D level, nor HER-2/neu expression varied significantly across age groups. Crude DFS and OS (unadjusted for other factors) were significantly worse for patients under age 30.

Table 1 shows the univariate linear trends analyses for the standard factors in just the node-positive population. More women under 30 had four or more positive nodes, T > 5 cm, and negative ER status. PgR was marginally significant. In addition, more tumors from women under 30 had high S-phase fractions ($P < .001$), but there was no correlation of age with ploidy, HER-2/neu, or cathepsin D. Crude 5-year DFS and OS were significantly worse in the youngest age group: 18% and 41%, respectively, for age less than 30, versus 60% and 73% for age 40-45 (with further improvement in older age groups).

The linear trends analyses for standard prognostic factors in the node-negative subset are shown in Table 2. Fewer women under age 30 had T1 tumors, and more had T3 lesions. More tumors in the youngest age group were ER- and PgR-negative. Considering new putative prognostic factors, significantly more patients under age 30 had tumors with high S-phase fractions, but ploidy status did not differ among age groups. There was no correlation of age with HER-2/neu or cathepsin D. However, Fig. 2 shows the striking percentage of tumors from patients under 30 and 30-35 that had abnormal p53 expression ($P < .001$). Neither crude 5-year DFS nor OS was significantly worse between younger versus older node-negative age categories.

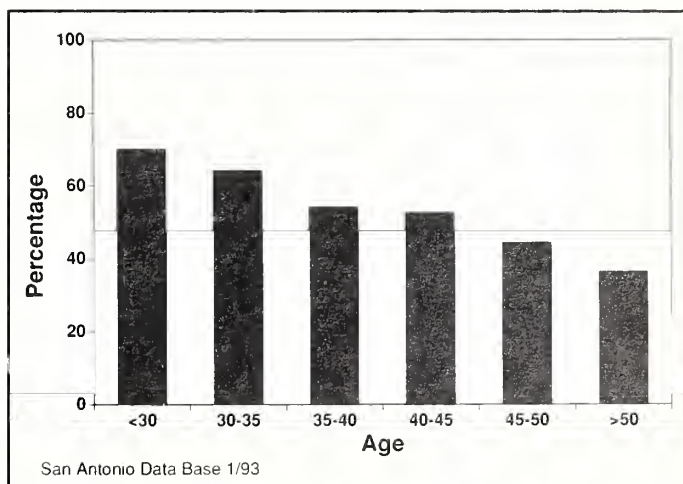


Fig. 1. Percentage of tumors with high S-phase fractions within each age category in the San Antonio database. P value was $< .001$ for the test for linear trend across age groups.

Table 1. Standard prognostic factors and age categories: patients with positive nodes*

Age group, y	≥ 4 positive nodes, %	T > 5 cm, %	ER-negative, %	PgR-negative, %
<30	72.6	37.8	54.9	60.9
30-35	53.3	22.6	49.6	55.0
35-40	54.8	27.1	37.3	46.0
40-45	48.1	19.3	33.6	41.1
45-50	50.8	19.1	28.4	41.3
>50	48.3	16.7	19.1	44.0
<i>P</i> -value, test for linear trend across age groups	.002	<.001	<.001	.042
Total No.	3948	3615	3929	3520

*San Antonio database, January 1993.

Table 2. Standard prognostic factors and age categories: patients with negative nodes*

Age group, y	T ≤ 2 cm, %	T > 5 cm, %	ER-negative, %	PgR-negative, %
<30	37.8	13.5	55.3	57.6
30-35	45.0	8.8	46.2	66.3
35-40	49.3	6.4	40.6	51.8
40-45	54.2	6.5	42.4	47.3
45-50	50.1	5.8	35.4	45.6
>50	55.4	5.3	18.2	45.0
<i>P</i> -value, test for linear trend across age groups	<.001	<.001	<.001	<.001
Total No.	4501	4501	4742	4126

*San Antonio database, January 1993.

Literature Review, Multivariate Analyses

The majority of cooperative group or consortium analyses that used multivariate models to assess for interactions included the age variable only as a dichotomy (<50 or premenopausal, postmenopausal). In most of these cases, neither age under 50 nor premenopausal status was an independent adverse predictor of outcome (11,12,17,22,25,35-37). Collectively, previous National Surgical Adjuvant Breast and Bowel Project node-positive analyses using the age 50 dichotomy concluded that grade was a much better discriminant of outcome than age (Redmond C: meeting communication, 1993).

Multivariate analyses that included other designations of young age (e.g., <35, <37, <40, etc.) with different mixes of standard variables generated conflicting conclusions regarding young age as an adverse independent predictor of outcome. Certain studies (19,20,24) reported younger age was a significant adverse factor along with various other discriminants; some (15,16,23,26,28) reported various independent adverse factors, but not young age; and others (18,22) either found several age categories with an independent adverse outcome or reported that older premenopausal status was an independent favorable predictor. There were no published multivariate analyses that used narrow age categories together with S-phase or other newer putative prognostic factors.

Three of these multivariate models will be reviewed in detail. First, the Milan node-positive series included only those patients treated with a mastectomy alone (no adjuvant therapy) (23). The subset under age 40 had the worst 10-year OS of any age group in univariate analyses. However, young age was not an independent discriminant of the poorest outcome in the multivariate analysis. Four prognostic groups were described with significantly different percent 10-year OS outcomes: age more than 40, one positive node (69.9%); age 40 or less (50.9%); age more than 40, two or more positive nodes, capsule intact (47.4%); and age more than 40, two or more positive nodes, extracapsular extension (25.3%).

The SWOG node-positive database differed from the Milan series in that all patients received uniform adjuvant chemotherapy, and two different multivariate methods were employed to assess for interactions among the factors (22). In the Cox models for DFS and OS, older premenopausal status was an independent predictor of a better outcome than postmenopausal or premenopausal under age 35. However, in a second analysis

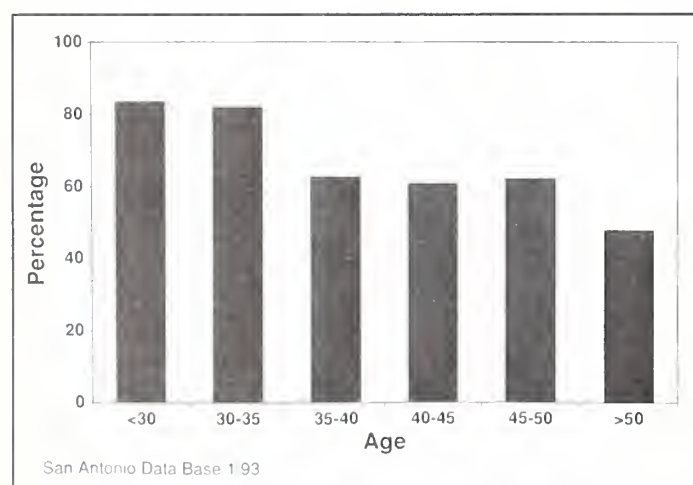


Fig. 2. Percentage of tumors with abnormal p53 expression within each age category in the San Antonio database. *P* value was <.001 for the test for linear trend across age groups.

[recursive partitioning and amalgamation (RPA)], discrete age cutpoints were not selected as significant descriptors. Instead, the number of positive nodes, menopausal status, tumor size, and age at menopause determined four prognostic categories for DFS; nodal status and receptor levels defined four subsets with different OS (22).

The third multivariate analysis was reported by the French group in a mixed node-negative and positive population; details regarding adjuvant therapy were not specified (19). Age less than 35 was an independent adverse factor. In a more recent analysis of just the node-negative subset, age less than 37, poor tumor grade, and large size were independent adverse predictors of DFS (20).

New San Antonio Analysis, Multivariate Models

Multivariate models were applied to the entire database, as well as to the node-positive and node-negative subgroups. The results of the first overall model with the standard factors of age, T size, ER, PgR, and number of positive nodes are shown in Table 3. After adjustment for the independent variables of more positive nodes, larger tumor size, and negative PgR, age under 30 remained a significant predictor of poor DFS (risk ratio for relapse relative to patients over 50 = 1.83). This adverse outcome was not due to "undertreatment" of younger women. In fact, the younger women in this database received adjuvant chemotherapy more often than older women, with or without adjustment for nodal status and tumor size.

Using these same standard factors, a Cox model was applied to the node-positive subset (1009 recurrences in 2879 patients). Independent adverse factors were high number of nodes, age under 30, large tumors, and negative PgR status. Table 4 shows the crude 5-year DFS and OS for the six age categories, as well as the same outcome measure *adjusted* for the independent variables. Even after adjustment, the 5-year DFS for an index case (three positive nodes, 3-cm tumor, ER-negative) was significantly worse for women under age 30. However, there was no significant difference for younger women when the OS was adjusted in a similar manner, and postmenopausal women had the poorest OS.

Table 5 gives the results of a similar Cox analysis in the subset with negative nodes (696 recurrences in 3617 patients). Age and tumor size were the only independent factors (ER and PgR

Table 4. Outcome by age category: patients with positive nodes*

Age, y	No. of patients	Crude 5-y DFS rate \pm SE	Adjusted 5-y DFS [†]	Crude 5-y OS	Adjusted 5-y OS rate \pm SE [†]
<30	46	18 \pm 7	33	41 \pm 9	64
30-35	108	46 \pm 6	57	60 \pm 6	69
35-40	215	49 \pm 4	56	62 \pm 4	73
40-45	295	60 \pm 3	63	73 \pm 3	65
45-50	404	61 \pm 3	63	69 \pm 3	70
>50	2471	56 \pm 1	58	65 \pm 1	52

*San Antonio database, January 1993.

[†]Adjusted for number of positive nodes, tumor size, and ER and evaluated for 3 positive nodes, 3-cm tumor, ER-negative.

Table 5. Outcome by age category: patients with negative nodes*

Age, y	No. of patients	Crude 5-y DFS rate \pm SE	Adjusted 5-y DFS [†]	Crude 5-y OS rate \pm SE	Adjusted 5-y OS [†]
<30	36	65 \pm 9	73	82 \pm 7	89
30-35	89	65 \pm 6	71	85 \pm 5	85
35-40	202	71 \pm 4	72	84 \pm 3	87
40-45	330	75 \pm 3	77	86 \pm 2	87
45-50	435	73 \pm 3	73	85 \pm 2	87
>50	3399	80 \pm 1	78	85 \pm 1	83

*San Antonio database, January 1993.

[†]Adjusted for tumor size and evaluated for 3-cm tumor.

were not). The 5-year DFS and OS outcomes for the youngest patients were not significantly different than the other age groups, once adjusted for tumor size.

The last Cox model returned to the entire database to assess ploidy status and S-phase in addition to standard factors and age categories (557 recurrences in 2587 patients). When ploidy and S-phase fraction were included as potential prognostic factors, both the length of follow-up developed substantially (median, 29 mo) because routine performance of flow cytometry is a relatively new technique. The findings are summarized in Table 6. As it was found in the first overall Cox model with only standard factors and age (Table 3), the nodal status, tumor size, and PgR were highly significant independent predictors of DFS. However, S-phase emerged as an important independent adverse predictor. None of the age categories was a significant factor in this smaller database regardless of whether S-phase fraction was

Table 3. Cox multivariate model for DFS with standard factors*

Prognostic factor	P	Risk ratio
Age, y		
<30	.0004	1.83 [†]
30-35	.28	1.16 [†]
35-40	.08	1.19 [†]
40-45	.38	0.92 [†]
45-50	.59	0.96 [†]
Square root positive nodes	.0001	1.35
Square root tumor size	.0001	1.56
PgR, + or -	.0016	0.84
ER, + or -	.08	0.90

*San Antonio database, January 1993; 1705 recurrences in 6496 patients.

[†]Risk relative to patients >50 years of age.

Table 6. Cox multivariate analysis for DFS*

Prognostic factor	P	Risk ratio
Square root positive nodes	.0001	1.343
Square root tumor size	.0001	1.602
PgR, + or -	.0016	0.761
Logarithm S-phase fraction	.0021	1.152
Ploidy (diploid or aneuploid)	.3721	—
ER, + or -	.6097	—
Age, y		
<30	.8318	—
30-35	.1779	—
35-40	.9572	—
40-45	.2497	—
45-50	.1021	—

*San Antonio database January 1993; 557 recurrences in 2587 patients.

included or excluded from the model. There were too few events and only a small number of patients to allow a separate node-negative Cox model with DNA and p53 data added to standard factors and discrete age categories.

Independent Outcome Predictors by Age Category

Few data were available regarding whether the actual *type* of independent outcome predictor differs depending on the age group. The Milan analysis found that number of positive nodes and presence of extracapsular nodal extension were significant discriminants for women over age 40 but that no standard factor was an independent predictor in those under 40 (23). In a "second look" at the SWOG node-positive database, exploratory Cox models for OS were done in each of the three age/menopausal status subsets. The number of positive nodes remained a significant predictor in each group, but receptor status lost significance for the premenopausal subset under age 35. This finding, could be due to the small sample size (Green S, O'Sullivan J: personal communication, 1/93). In the M. D. Anderson analysis, there was no difference in outcome whether zero, one, two, or three nodes were positive in women less than 30, versus a distinct survival difference for the discrete nodal groups of age 30 years or more (21).

The San Antonio database was analyzed in this regard, as shown in Table 7. In a Cox model for patients under age 35, the number of positive nodes was the only independent adverse predictor, with a very high relative risk. However, the number of patients available for this analysis was very small, and important contributions from other factors could easily have been missed. In women aged 35-50 years, only the number of involved nodes and T size, both with lower relative risks, were significant predictors of recurrence.

Discussion

This investigation provides some answers to the four original questions regarding breast cancer outcome and younger age.

Table 7. Cox multivariate analyses for DFS in the 2 youngest subsets of patients*

Prognostic factor	P	Risk ratio
<i>Patients <35 y†</i>		
Square root positive nodes	.0001	1.562
Square root tumor size	.2173	—
Logarithm S-phase fraction	.2613	—
Ploidy (diploid or aneuploid)	.7026	—
PgR, + or -	.7893	—
ER, + or -	.9690	—
<i>Patients 35-50 y‡</i>		
Square root positive nodes	.0001	1.230
Square root tumor size	.0247	1.403
PgR, + or -	.1058	—
Logarithm S-phase fraction	.2370	—
Ploidy (diploid or aneuploid)	.2360	—
ER, + or -	.3080	—

*San Antonio database, January 1993.

†25 recurrences in 84 patients.

‡158 recurrences in 635 patients.

The first question, "Is breast cancer outcome worse in the youngest age subset?", ideally must be answered from population-based data. Thus, possible biases inherent in single institution or cooperative group series are removed, such as referral or study-specific accrual patterns and specific treatment and protocol entry requirements. Caveats regarding these population-based data merit mention, with a focus on those series that considered narrowly defined age categories. The outcome measures employed (DFS, OS, or both) were variable, none reported OS adjusted for noncancer deaths, and adjustments were made for expected mortality in only a few reports. There was no control for use and/or type of adjuvant therapy. The two major stage breakdowns used (local versus regional or I versus II versus III) were either defined differently across the trials (only a minority utilized current nomenclature), or there was no adjustment for stage. The influence of socioeconomic status and race variables were not considered. None of the large, population-based analyses employed multivariate methodology to rule out possible interactions between young age and other factors.

Nevertheless, these population data collectively suggested that the very young subset did worse. This especially was the case when only those reports were considered that carefully defined stage and then analyzed outcome by age category within a specific stage or node subset. The results were nearly unanimous regarding a worse outcome for women under age 30-35 in the "regional" or positive-node disease cohort. The reports were less consistent in the "local" or node-negative stage subset.

The second question originally raised follows naturally from this first conclusion: "Are adverse predictors of outcome more prevalent the younger the patient?." Unfortunately, population-based data did not provide a clear answer to this query. Several more limited population-based analyses found that significantly more younger women presented with advanced "stages," whereas other similar studies noted no difference in the stage distribution across age groups. However, most reports did not provide data regarding age distribution of either the number of positive nodes or other known predictors.

Therefore, despite potential bias, it was necessary to search larger referral populations for additional data regarding young age and prognostic factor distribution. Many reports suggested that the premenopausal (or age <50) subset had a greater frequency of positive nodes, high tumor grade, large tumor size, or negative receptors. Unfortunately, very few of these analyzed for more than one factor, nor were narrow age categories used. Furthermore, the younger subgroup was often too small for subset analysis (11). The SWOG node-positive analysis explored univariate distributions of a number of factors in three age categories (22). Women under 35 more often had more than six positive nodes, but no other factor had a different distribution by age in this select population.

The San Antonio database provided a unique opportunity to gain new insight regarding this second question. Both standard prognostic factors and new, potential variables were available. Furthermore, because the sample size was quite large, narrow age categories were defined for the univariate trends analyses. Women under age 30 had significantly more number of positive nodes and negative receptors and larger tumors. However, two other findings provided additional clues as to why younger

women with breast cancer collectively do worse. A greater percentage of tumors with high S-phase fractions was correlated with decreasing age. The p53 data in the node-negative subset were even more striking: over 80% of the tumors from women less than 30 years and over 80% from women of ages 30-35 had abnormal accumulation of mutant p53 protein. In a recent San Antonio node-negative multivariate analysis, the only independent adverse predictors of DFS were abnormal p53 (greatest significance) and high S-phase fraction (12). Thus, the most attractive explanation for the conclusions of the population-based series might be a greater frequency distribution of high S-phase and abnormal p53 in women under age 30.

The multivariate models that included narrow age categories provided additional support for this explanation, as well as answered the third question, "Is age an intrinsic *independent* adverse predictor of DFS and OS, or is outcome worse in younger women due to poor prognostic factor profiles?." A few caveats regarding these models must be considered. Very few used databases with uniform adjuvant treatment, and most did not consider histologic variables along with the standard and newer prognostic factors. Adjustments were usually not made for expected mortality, noncancer deaths, or age-specific trends in response to treatment on relapse. These studies were not designed to prospectively assess the younger age group, which in most cases was very small in number. Instead, these analyses were performed in select populations due to the intrinsic requirements of study design and eligibility. For example, patients with tumors too small for standard receptor measurement were usually excluded from most cooperative group studies and tumor bank databases. It is also important to consider how age was represented in the analyses. Most often age was considered a proxy variable for menopausal status and, therefore, was dichotomized at 50 years. This categorization would contaminate any effects in the very young with that of older patients, including some young postmenopausal women. Other studies represented age as a continuous variable in the analyses. This assumed that a monotone (usually linear) relationship existed between age and the factor under study. In the case of DFS or OS, this may not be an appropriate assumption. Thus, for all these reasons the conclusions regarding younger age from multivariate models should be viewed only as exploratory or hypothesis-generating.

With these disclaimers in mind, the multivariate analyses reviewed and presented herein suggested an answer to the third question. Young age at diagnosis was not consistently retained as an independent adverse predictor across all the models. Adjustment for independent prognostic variables often resulted in a loss of the outcome differential by age. It appeared that young age was retained in those models where only a few, standard prognostic factors were included, whereas it often lost independent variable status in other models when either more standard variables or S-phase fraction data were available. This latter phenomenon was demonstrated in the San Antonio analysis (Tables 3 and 6). Either a high % S-phase, high tumor grade, or abnormal p53 was among the strongest independent discriminants within other node-negative analyses [(11,12,20); Redmond C: meeting communication, 1993]. Finally, neither the Milan nor the SWOG analyses retained youngest age as a

descriptor among the Cox or RPA-determined poor prognosis groups (22,23). Thus, across all analyses, young age was not a consistent independent predictor of poor outcome but instead often served as a surrogate variable for an adverse prognostic factor profile.

The last question, "Are independent predictors of DFS or OS similar or different across various age groups?," could not be answered with certainty due to limited published data. No study has yet demonstrated that the *type* of predictor of relapse or death is *different*, depending on the age at diagnosis. However, exploratory multivariate analyses of the SWOG, Milan, and San Antonio databases provided insight [(22,23); this analysis]. The presence or absence of positive nodes was the most important independent discriminant in all ages. However, other standard prognostic variables such as tumor size, ER, PgR, or number of positive nodes were not consistently predictive in the youngest subset. For example, in this investigation, the square root of the number of positive nodes was the only significant adverse independent predictor in women under age 35, whereas tumor size was also important in the age 35-50 subgroup (Table 7).

Our conclusions regarding poor outcome in the youngest age group (due to a greater likelihood of an adverse prognostic factor profile) alter some commonly held viewpoints. It is often said that younger women with breast cancer do worse because they present with later stages of disease, due to either physician or patient delay in diagnosis. This may occur in specific cases. However, the stage-matched population data, the univariate and multivariate analyses in both node-negative and positive groups, as well as the striking incidence of abnormal p53 in the youngest *node-negative* subsets collectively suggest that there may be a different biology of this disease in the youngest cohorts. In addition, many propose that the younger subset does worse because there is less chemotherapy-induced menopause. None of the multivariate models that include the very young cohort address this issue. However, the presence of more adverse predictors in the younger node-negative subsets compared to all other ages with negative nodes indirectly addresses this question. The majority of these data antedated the adjuvant therapy era for negative nodes. Thus, the outcome findings cannot be explained by less treatment-induced ovarian failure.

The answers to the four questions posed at the start of this investigation suggest possible directions for future research regarding breast cancer outcome and predictors of outcome in younger women. Research emphasis and funding could be directed to further study of existing databases, as well as to formation of retrospective data "pools" of young cases, prospective databases, and tumor banks. For example, existing population bases could be reanalyzed, using the node subsets in current use and with the addition of other available prognostic factors. Or clues might be gathered from further study of the recurring observation that older, postmenopausal women consistently have the best outcome in various stage subsets [(5-7,18,22); this investigation]. For all future analyses, disease-free survival must be assessed, and survival data should be adjusted for noncancer deaths and for expected mortality. Multivariate models could be applied to the large populations using narrow age categories, such as the vast international database of the Early Breast Cancer Trialists' Cooperative Group (39). Networks of tumor banks

could be formed, in conjunction with a prospective population-based trial, in order to increase the pool of the youngest subsets. Thus, one could design translational research targeted on standard and newly defined prognostic factors, together with genetic abnormalities at a molecular level, within narrow age categories in uniformly staged and treated patients.

Therefore, in this way, basic, clinical, and translational research can merge onto a search for reasons why the prognostic factor profile in the youngest cohorts is more often weighted with adverse outcome predictors, even in the node-negative subset. It is critical that attention is given to the p53 data. If this finding is confirmed, the possible interactions of this suppressor gene with the unique hormonal milieu of the younger patient, as well as with breast cancer susceptibility gene abnormalities, must be explored in depth.

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Patterns of Care for Younger Women With Breast Cancer

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Although breast cancer tends to be a disease of older women, the disease also affects premenopausal women with potentially devastating personal and financial consequences. To identify features of the disease that are important to younger women, and to describe the current treatment practices as applied to younger women, data from the 1991 Patient Care Evaluation Breast Survey by the Commission on Cancer of the American College of Surgeons were analyzed by age cohort. The 1991 survey, the third breast cancer survey by the Commission on Cancer since 1972, obtained information on patterns of care nationwide using the Commission's hospital tumor registry system (1,2).

Materials and Methods

Hospitals with cancer registries were invited to participate in a long-term study of patients whose diagnosis of breast cancer was made in 1983 and a short-term study of patients whose diagnosis was made in 1990. For each study year, hospital tumor registrars were asked to complete questionnaires for 25 consecutive patients who had their diagnosis and all or part of a first course of treatment at the reporting hospital. Registrars were instructed to use data from the registry abstract, the hospital records, and other available clinical charts. Pathologic diagnoses were entered according to the International Classification of Diseases for Oncology Codes (ICD-0) (3). Diagnoses other than infiltrating and in situ carcinomas were excluded. The pathologic TNM staging system was used as defined in the 1988 *Manual for Staging of Cancer*, third edition (4). Completed data forms were reviewed at each hospital by a member of the hospital cancer committee before they were returned to the Cancer Department of the American College of Surgeons for collation and analysis. The 1990 data were analyzed for patterns of care for younger patients with breast cancer and are presented in this report.

Results

Data on 24 356 patients from 1011 hospitals were submitted for the 1990 study. Data edits resulted in elimination of 382 cases, leaving 23 974 cases for analysis. Hospitals from all 50 states, Puerto Rico, and Canada participated.

Table 1 shows the ages of patients in this study. The median age was between 60 and 64 years, with 76% of the patients over the age of 50.

Table 1. Patterns of care for young women with breast cancer

Age, y	No. of patients (%)
≤30	208 (0.8)
31-40	1594 (6.6)
41-50	3969 (16.6)
>50	18 203 (75.9)
Total	23 974

The tumor size and pathologic TNM stage at presentation are shown in Tables 2 and 3. Fewer young patients presented with small (<2 cm) cancers. Whereas 48.2% of women over the age of 50 years had tumors less than 2 cm, only 29.7% of women 30 or younger had tumors less than 2 cm. Conversely, 49.5% of women 30 years or less had tumors larger than 2 cm compared to 30.8% for women over 50 years of age. Although inflammatory carcinomas were uncommon in all age groups, fivefold more women 30 years of age or less had inflammatory carcinomas compared with women over 50 years of age. These data indicate that the diagnosis was made later in the course of the disease in younger women.

A related observation is shown in Table 4. Younger women appeared to have had fewer diagnoses of nonpalpable lesions made by mammogram-directed biopsies.

Most patients were treated by surgery. The type of operation performed, as related to stage for the entire population, is shown in Table 5. Most patients were treated by modified radical mastectomy. As shown in Table 6, women in the younger age group

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See "Note" section following "References."

Table 2. Pathologic TNM stage distribution by age

Stage	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
0	4.8	7.5	9.8	7.2
I	20.2	28.4	30.8	38.5
IIA	26.4	26.3	25.6	22.6
IIB	24.0	17.6	15.1	11.3
IIIA	8.2	6.6	5.1	3.3
IIIB	2.9	2.4	2.6	3.6
IV	5.8	2.6	3.2	3.5
Unknown	7.7	8.7	7.8	10.1
Total	100.0	100.1	100.0	100.1

*208 patients.

†1594 patients.

‡3696 patients.

§18 203 patients.

Table 3. T size distribution by age

T size	% distribution by age			
	≤30 y	31-40 y	41-50 y	>50 y
In situ	5.3	7.8	9.9	7.2
<2 cm	10.1	11.9	12.5	14.2
≤0.5 cm	1.9	2.1	3.1	3.2
>.5 ≤1.0 cm	1.4	5.5	6.4	9.7
>1 ≤2 cm	16.3	20.1	18.9	21.1
>2 cm ≤5 cm	40.4	33.4	31.5	27.0
>5 cm	9.1	8.0	5.9	3.8
T4	3.4	2.0	3.0	4.5
Inflammatory	2.9	0.7	0.9	0.6
Unknown	9.1	8.3	7.7	8.4
Total	99.9	99.8	99.8	99.7

Table 4. Mammogram-directed biopsy distribution by age

Biopsy	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
Yes	4.3	8.5	13.9	16.0
No	81.7	79.8	76.1	74.7
Unknown	13.9	12.8	10.0	9.3
Total	99.9	101.1	100.0	100.0

*208 patients.

†1594 patients.

‡3969 patients.

§18 203 patients.

with early-stage (0 or I) disease were treated more frequently by partial mastectomy than older women. Women over 50 years of age had fewer lymph node dissections performed with the partial mastectomies. As shown in Table 7, 22.3% of women 30 years of age or younger were known to have had reconstructions compared to 7.5% in the total population and 4.4% of women older than 50 years of age.

Little difference was seen in the use of radiotherapy in different age groups, with a slightly higher percentage of women less than 50 years of ages receiving radiation (Table 8). As shown in Table 9, few women had radiotherapy after simple or

Table 5. Relationship of stage to type of surgery

Surgery	Stage, %					
	0*	I†	IIA‡	IIB§	IIIB	IV¶
<Total, no nodes#	22.2	4.7	2.5	1.1	1.2	19.4
<Total, nodes**	7.9	19.8	11.9	8.2	3.6	5.7
Simple	11.0	2.0	2.2	1.3	4.0	8.5
Modified radical	52.4	71.1	81.1	87.6	83.4	39.6
Radical	0.4	0.5	0.9	1.0	2.6	1.8
Other	2.3	0.7	0.6	0.3	0.8	2.7
Unknown/not otherwise specified	3.7	1.2	0.8	0.5	1.1	22.2

*2484 patients.

†13 600 patients.

‡10 614 patients.

§5871 patients.

||3263 patients.

¶1733 patients.

#Includes partial mastectomy, quadrantectomy, or lumpectomy without a lymph node dissection.

**A lymph node dissection was performed.

Table 6. Type of surgery by age—stage 0 and I

Surgery	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
<Total, 0 nodes	9.6	5.9	9.6	8.3
<Total, nodes¶	26.9	32.2	28.1	20.8
Simple	7.7	2.8	3.5	3.0
Modified radical	51.9	55.8	55.5	65.4
Radical	0	0.5	0.2	0.2
Unknown/not otherwise specified	3.8	2.8	3.1	2.5
Total	99.7	100	100	100.2

*52 patients.

†572 patients.

‡1612 patients.

§8306 patients.

||Includes partial mastectomy, quadrantectomy, or lumpectomy without a lymph node dissection.

¶A lymph node dissection was performed.

Table 7. Distribution of postmastectomy reconstruction by age

Reconstruction	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
Yes	22.3	20.2	15.9	4.4
No/unknown	77.7	79.8	84.1	95.6

*197 patients.

†1526 patients.

‡3789 patients.

§17 320 patients.

modified radical mastectomy. Patients who had had lymph node dissections with a partial mastectomy tended to have radiotherapy.

A large proportion of young patients received cytotoxic chemotherapy (Table 10) and 71% of older patients received tamoxifen (Table 11). Interestingly, approximately 10% of patients less than 30 years of age also received tamoxifen.

Table 8. Distribution of radiotherapy by age

Radiotherapy	% distribution, by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
Yes	26.9	27.9	26.7	20.5
No	64.4	64.2	66.3	72.7
Patient refused	1.0	1.6	0.9	1.3
Unknown	7.7	6.2	6.1	5.5
Total	100.0	99.9	100.0	100.0

*208 patients.

†1594 patients.

‡3969 patients.

§18 203 patients.

Table 9. Radiotherapy and surgery—all ages

Type of surgery	No. of patients	Radiotherapy, %			
		Yes	No	Refused	Unknown
<Total, no nodes*	2185	28.3	59.7	3.3	8.6
<Total, nodes†	3973	77.1	17.5	1.0	4.5
Simple	787	8.4	84.0	1.7	6.0
Modified radical	15 984	7.4	86.6	0.7	5.3

*Includes partial mastectomy, quadrantectomy, or lumpectomy without a lymph node dissection.

†A lymph node dissection was performed.

Table 10. Distribution of chemotherapy by age

Chemotherapy	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
Yes	67.8	59.9	53.2	43.8
No	22.1	31.9	38.2	47.3
Patient refused	2.4	1.5	1.5	1.7
Unknown	7.9	6.7	7.1	7.3
Total	100.2	100.0	100.0	100.1

*208 patients.

†1594 patients.

‡3969 patients.

§18 203 patients.

Table 11. Tamoxifen treatment distribution by age

Tamoxifen treatment	% distribution by age			
	≤30 y*	31-40 y†	41-50 y‡	>50 y§
Yes	9.9	17.9	30.1	71.2
No	75.2	66.9	56.5	21.4
Unknown	14.9	15.2	13.5	7.4
Total	100.0	100.0	100.1	100.0

*141 patients.

†955 patients.

‡2113 patients.

§7969 patients.

Discussion

Some potential limitations of these data should be noted. This is a convenience sample from a hospital-based registry system, not all-inclusive data from a population-based registry. Although the registrars who answered the questionnaire were instructed to seek information outside the hospital record when necessary, preadmission and postdischarge data were obviously more difficult to capture than the information in the hospital record. Less than 9% (Tables 8-11) of patients were listed as unknown with regard to receiving radiotherapy or chemotherapy. Data were unknown for as many as 15.2% of patients with regard to receipt of tamoxifen.

The age distribution of patients in this study was similar to the Commission on Cancer's 1982 Patterns of Care Study in which less than 1% of patients were less than 30 years of age and approximately 25% were less than 50 years of age (2). Similar age distributions have been reported by SEER (5).

The data from this study agree with other studies showing that young patients present with more advanced-stage disease (6,7). The fraction of young women who presented with small tumors was approximately 20 percentage points less than patients over the age of 50. A number of factors may contribute to the later diagnosis of young patients. Most breast abnormalities in young patients are benign. The breast tissue is frequently dense and difficult to evaluate by physical examination or by mammography (8). The breast tissue fluctuates in response to cyclic hormone changes making "thickening" and nodularity commonplace.

The impact of mammographic screening is difficult to estimate in any population and particularly difficult in young women. The higher stage of presentation for young women reported in this study suggests that mammographic screening may be having a smaller impact on this group than on older women. Only 3.3% of women under 30 years in our study had lesions less than 1 cm compared to 12.9% of women over 50 years. The American Cancer Society guidelines, at the time of diagnosis of this study population, recommended a baseline mammogram at age 35, but did not recommend routine mammographic screening before the age of 40. The number of women under the age of 35 who have screening mammograms is unknown but probably small.

White et al. (9), using SEER data from Western Washington State, have argued that mammographic screening could account for an increased incidence of breast cancer in women aged 45-64, but could not account for the 29% increase in women aged 25-44. Since the mammography data for that study did not apply directly to the study population and because the age cohorts selected overlap the American Cancer Society age guidelines, it is difficult to interpret the assertion.

One indication of the impact of mammography is the number of mammographically directed biopsies of nonpalpable lesions. Such lesions can only be identified by mammography. Although questions were included in our study regarding screening mammography as the first indication of disease, it was difficult to obtain such information from the hospital record and the data were not analyzed by age cohort for this paper. Obviously, some patients had lesions detected by mammography that were pal-

pable when these patients were subsequently examined. Therefore, the rate of mammographically directed biopsy is the most accurate measure of the impact of screening mammography available from our data. The fraction of patients over the age of 50 years who were known to have had mammographically directed biopsies was almost four times the percentage of women 30 or younger who had had similar biopsies. It is not clear how patients younger than 35 years of age, for whom screening mammography is not recommended routinely, came to a mammographically directed biopsy. Investigation of that group might yield information leading to recommendations for early detection in young patients.

The desirability of breast-conserving surgery for patients of any age is understandable from a cosmetic and psychologic point of view. The partial mastectomy rate has risen from 3.4% in the first breast-patient care evaluation study by the Commission on Cancer in 1972 to 13.1% in 1983 in the second study and to 25.4% in the 1990 study (1,2). These changes have occurred as radical mastectomy has virtually disappeared and been replaced by modified radical mastectomy. Further evidence for interest in cosmetic outcome is also indicated by the fivefold rate of reconstruction in young patients when compared to women over the age of 50.

The higher recurrence rates in the breast that have been reported for young women after breast-conserving surgery are alarming (10-12). Boyages et al. (10) reported a high risk of breast recurrence after partial mastectomy and radiation therapy when an extensive intraductal component was associated with an invasive cancer in very young women defined in that study as 34 years of age or younger. Although there was an association of young age with the extensive intraductal component, the two factors appeared to be independent variables. Kurtz et al. (11) found the same association between young age and local breast recurrence, but their data supported the view that age dependence of the histologic factor (extensive intraductal component) explained the high local failure rate. Nemoto et al. (12) also reported a major increase in local failure rate in patients who were treated by lumpectomy without radiation therapy. These studies suggest that breast-conserving surgery may not be applied with equal safety to all age groups.

The use of adjuvant therapy seen in this report generally follows the guidelines of the NIH Consensus Conference that

recommended the use of chemotherapy in premenopausal node-positive women and the more recent Clinical Alert that recommended chemotherapy for node-negative patients (12,13).

In summary, this Patterns of Care Study by the Commission on Cancer of the American College of Surgeons indicates that, compared to older patients, young women presented with more advanced disease, had a lower rate of mammographically directed biopsies, were treated more commonly by partial mastectomy or breast reconstruction after total mastectomy, and frequently received chemotherapy.

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Note

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Section III: Screening and Prevention

*Elizabeth A. Patterson**

Breast cancer is not a common disease in women under the age of 35, which is the usual and publicized age to begin routine screening mammography. It accounts for only about 2% of all cancers (1).

Although the mortality rate is low, it is the leading cause of cancer mortality in women ages 15-35. It has been stated that because of the very low prevalence of breast cancer in young women, screening in this low-yield age group is expensive and diverts manpower from the more important task of screening and diagnosis in older women. The role of screening mammography is, therefore, very controversial and there are no guidelines that currently exist.

A recent survey by Homer (2) showed that most mammographers throughout the country do not perform screening examinations in women under the age of 35, although this age limit is lowered in women with significant risk factors. Some mammographers suggested that screening should begin at the age of 30 in women who have a primary relative with breast cancer.

Several factors have contributed to the hesitancy of using breast-imaging studies in women under the age of 35. These, include the relative density of the breast in the younger age group with the general belief that mammography is less accurate and, therefore, not useful, as well as the sensitivity of the young breast to radiation (3).

Because of these factors, a delay in diagnosis is significant in the young age group. In one study (4), there was a 3-month delay in diagnosis in the young patients in 45% of their breast cancers and up to a year delay in 12% of the patients.

Another study from the United Kingdom (5) showed that the average symptoms before the diagnosis was 26 weeks and only 28% had early-stage stage I breast cancer.

In an attempt to avoid delay in diagnosis of breast cancer yet promote effective screening, we will consider several issues:

Who is at risk for breast cancer in this young age group?

Are there any genetic or other biological markers to indicate what women are at high risk?

How should we screen these individuals at risk?

What studies do we have to indicate when we should screen, and at what interval?

What breast-imaging studies should we perform and what are the indications for performing these studies?

And finally, is there any way of preventing breast cancer, specifically addressing the young women with risk factors?

What potential methods are present? What preventative factors might we enhance or what causative factors could we eliminate?

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Genetic Epidemiology of Breast Cancer in Younger Women

Elizabeth B. Claus*

Genetics plays a role in all of breast cancer. At present, however, inherited genes associated with the development of breast cancer have more frequently been identified in women with an early age at onset. This review examines the extent to which genetic information, at both an epidemiologic and molecular level, may be used to identify a subset of women who are likely to be at increased risk of developing breast cancer at an early age. [Monogr Natl Cancer Inst 16:49-53, 1994]

It is well known that a family history of breast cancer is associated with an increased risk of developing breast cancer (1-18). In fact, among those variables that have been shown to bear a relationship with breast cancer, the greatest increase in risk, after controlling for age, has generally been associated with the presence of a positive family history (5,6,12,14). Within this group of women with a positive family history, the most important factors determining the risk of breast cancer are the number and types of relatives affected with breast cancer, along with the ages at which these relatives became affected. In general, a first-degree family history of breast cancer is associated with an approximate twofold to threefold increase in the risk of breast cancer (6,12,17,18), while a history of breast cancer in a second-degree relative has been associated with a risk approximately half that of women with an affected first-degree relative (12,17). Women with two or more first-degree relatives affected with breast cancer show an increase in the risk of developing breast cancer (12,15,20). This risk increase is reported to be 2.5 to 14 times that of a woman without an affected relative. Furthermore, although not all studies concur (21), it has generally been found that the risk to a woman increases with decreasing age at onset of any affected relatives (6,17,18). Women with multiple relatives diagnosed with breast cancer at an early age are at particularly high risk (1-3,6).

A woman's risk of developing breast cancer also appears to be associated with the diagnosis of ovarian cancer in a first-degree family member. Epidemiologic studies show approximately a 50% increase in the risk of breast cancer among women who report a family history of ovarian cancer versus those who do not as well as a similar increase in the risk of ovarian cancer among women who report a family history of breast cancer (22-24). These studies have reported some variation in risk by age at onset of the cancer case, but this variation is not statistically significant (22,23). In addition to these epidemiologic studies, recent linkage analyses point clearly to

the existence of a genetic relationship between breast and ovarian cancer in some families (1,4).

Although the findings are not uniform across studies (25), there is evidence that the presence of bilateral breast cancer in a first-degree relative may increase a woman's risk of developing breast cancer over that of a woman with a first-degree relative affected with unilateral breast cancer (9,10,20,26). In a recent follow-up study of the 4730 breast cancer cases of the Cancer and Steroid Hormone study (CASH) (27), the risk of contralateral breast cancer was elevated almost twofold among breast cancer cases who reported a first-degree family history of breast cancer (26), a value similar to other positive studies. A number of researchers have examined the effect of age at onset on the relationship between a woman's risk of breast cancer and the presence of bilateral breast cancer in a first-degree relative and found that relatives of younger breast cancer cases with bilateral disease are at increased risk (9,10), although, once again, this finding is not universal (20,21). Of further interest is the fact, in the CASH data (27), that the increase in the risk of contralateral breast cancer in women with a positive family history of breast cancer did not vary by age at diagnosis of the first primary cancer, at least not in the first few years after diagnosis. This is unlike the situation for first primary breast cancer, since the risk associated with having a first-degree relative with breast cancer is much higher in younger women than it is in cases with a later age at onset. Continued follow-up of the CASH cases as well as additional prospective studies of breast cancer cases of all ages at onset will be necessary to further define the association between bilateral breast cancer and a family history of breast cancer, particularly with regard to age at onset (26).

The patterns of recurrence risks observed among the relatives of breast cancer cases in epidemiologic studies are consistent with a genetic model. More formal genetic analyses corroborate the genetic hypothesis. The majority of segregation analyses of breast cancer pedigrees has provided evidence for the existence of one or more rare autosomal dominant genes leading to increased susceptibility to breast cancer (27,28-31), including a recent segregation analysis of the 4730 breast cancer cases from the CASH study (27). In this study, the increase in risk to carriers versus noncarriers increases with decreasing age, indicating that younger breast cancer cases are more likely to represent

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See "Notes" section following "References."

gene carriers than are older breast cancer cases. The proportion of cases predicted to carry the breast cancer susceptibility allele among breast cancer cases aged 20-29, 30-39, and 40-49 is estimated to be 33%, 22%, and 14%, respectively (Claus EB, Schildkraut JM, Thompson WD, et al: manuscript submitted for publication).

The results of segregation analyses have been confirmed by recent linkage analyses. These analyses provide strong evidence for the existence of a breast cancer susceptibility gene (or genes) located on the long arm of chromosome 17 (1-4). In the families for whom linkage has been found, the transmission of breast cancer is consistent with an autosomal dominant inheritance pattern. In addition, in these families, the disease often occurs at a young age and in association with ovarian cancer. Hall et al. (2), the first group to report linkage of breast cancer to chromosome 17q21 found particularly strong evidence of linkage in families with an early age at onset. When only families with an average age at onset less than 46 years of age were used, the odds in favor of linkage were estimated to be approximately 10^6 to 1. In 1991, Narod et al (4) showed that both breast and ovarian cancer were linked to chromosome 17q12-23 by examining five families characterized by multiple cases of early-onset breast and ovarian cancer. The authors did find evidence of genetic heterogeneity, however, as only three of the five families appeared to be linked to chromosome 17. In this analysis, linked and unlinked families did not differ in their age at onset distribution; the median age at onset of the women with breast or ovarian cancer was below 45 and 49, respectively, in all five families.

In an effort to confirm the aforementioned linkage results as well as to attempt to localize a breast cancer gene, called BRCA1, members of the Breast Cancer Consortium (1) recently analyzed 214 extensive breast cancer pedigrees, including 57 families characterized by both breast and ovarian cancer (hereafter defined as breast/ovarian families). In this series of families, the members of the Consortium found striking evidence of linkage; the odds in favor of linkage to chromosome 17q21 are estimated to be over 10^{21} to 1. In the 57 breast/ovarian families, most show evidence of linkage to chromosome 17q21, suggesting that a gene (or genes) on chromosome 17 accounts for the majority of families in which both early-onset breast cancer and ovarian cancer occur. Approximately 45% of the families containing breast cancer cases only were linked, indicating that additional loci are likely to be involved in the development of breast cancer. As was true in the Hall et al. (2) analysis, the proportion of linked cancer cases varied by average age at onset. When only families with an average age at onset of less than 45 years were included, an estimated 67% were linked, compared with 19% and 38% of families with an average age at onset between 45 and 55 years and greater than 55 years, respectively (1).

The information gathered from the above-mentioned analyses may be used in counseling young women likely to be at increased risk due to their family histories of breast cancer. In particular, it is of interest to estimate not only the overall increase in the lifetime risk of breast cancer to a woman with a family history of breast cancer but also the extent to which a woman's family history places her at increased risk for developing the

disease at an early age. This is particularly important in light of the aggressive nature of many breast cancers found in young women. A number of investigators have attempted to address this issue and have included age-specific risk estimates for young women in their studies (1,9,19,20,32,33). Several of the most recent studies are reviewed here.

Ottman et al. (9) provide breast cancer risk estimates for women with one first-degree relative affected with breast cancer. Using cumulative risks, the authors derive the probabilities of developing breast cancer within a specified age interval for mothers and sisters of women diagnosed with breast cancer. The probabilities are presented by the age at onset as well as the laterality status of the breast cancer case. In these tables, the risks of developing breast cancer at a young age are estimated to be higher for sisters than for mothers. Mothers and sisters of unilateral breast cancer cases diagnosed by the age of 50 are shown to have a risk of 0.7% and 4.8%, respectively, of themselves developing breast cancer by age 50 compared with risks of 1.5% and 5.2% if the case was diagnosed after age 50. The risk of developing breast cancer before the age of 50 years for a woman with a first-degree relative affected with bilateral breast cancer is estimated to be extremely high, particularly if the relative herself was diagnosed at a young age. The risk of breast cancer to age 40 and 50 for the sister of a bilateral case diagnosed by age 40 is estimated to be 7.7% and 23.5%, respectively, versus 4.9% and 9% for the sister of a bilateral breast cancer case diagnosed between the ages of 41-50. Mothers of bilateral cases had similar although slightly lower risks.

A second study (20) presents similar information for women with two or more relatives diagnosed with breast cancer. Specifically, the authors present the probabilities of developing breast cancer within a specified age interval for sisters of breast cancer cases whose mother, sister, or second-degree relative was also affected. The risk of a sister of a unilateral case developing breast cancer by age 40, regardless of pedigree type, was 1%. The risk of a sister of a unilateral case developing breast cancer by age 50 was approximately 7.0% if an additional first-degree relative was affected or 2.0% if a second-degree relative was affected. In general, the risks to sisters of bilateral cases were higher, although the interpretation of these numbers is complicated by the fact that the sample size was relatively small.

A recent large study (33) presents detailed breast cancer risk tables for women with one or more first- and/or second-degree relatives diagnosed with breast cancer. The risks in this study are obtained using the results of segregation analyses performed on the CASH data (27). The probabilities of developing breast cancer are presented by the number and types of affected relative as well as by the ages at which those relatives were diagnosed with breast cancer. Under the CASH model, the risk of a woman with a positive family history developing breast cancer at a young age is predicted to be increased over that of a woman of the same age without a family history, but they are lower than those predicted for women who carry the BRCA1 gene. For example, a woman with a first-degree relative diagnosed with breast cancer in her 30s is predicted to have a 0.5%, 1.7%, and 4.4% chance of developing breast cancer by age 29, 39, and 49 years, respectively. A woman with a first-degree relative diagnosed with breast cancer in her 70s is predicted to have a 0.1%,

0.5%, and 1.5% chance of developing breast cancer by age 29, 39, and 49, respectively, rates that are similar to those seen in the general population. For a woman with two first-degree relatives, both of whom were diagnosed with breast cancer in their 30s, these same risks are estimated to be 1.8%, 6.2%, and 14.8% compared with 0.2%, 0.8%, and 2.3% for a woman with two first-degree relatives diagnosed in their 70s. Since the CASH estimates are based on population-based data, they are likely to include the effect of the BRCA1 gene. The risks for women who do not carry the BRCA1 gene are, therefore, likely to be slightly lower than those presented here; the extent, however, to which the presence of the BRCA1 gene affects these estimates will need to be further quantified once population-based estimates of its prevalence are obtained.

Two additional studies have produced valuable models that may be used to estimate a woman's risk of developing breast cancer within a specified age range. The first of these studies, the linkage analysis study of the Breast Cancer Consortium Group [(1) and Easton DF, Ford D, Bishop DT, et al: manuscript submitted for publication] presents risk estimates based solely on genetic parameters, i.e., on the knowledge that a woman does or does not carry the deleterious BRCA1 gene. These estimates indicate that the probability of developing breast cancer at an early age for women who carry the BRCA1 gene is extremely high. Assuming no heterogeneity of risk between linked families, the BRCA1 allele is estimated to confer a breast cancer risk of 3%, 19%, and 51% by age 30, 40, and 50, respectively (Easton DF, Ford D, Bishop DT, et al: manuscript submitted for publication). Of note, however, is the fact that these authors have found evidence of heterogeneity of risk between families and report that if one fits a model with two BRCA1 alleles, then the risk of developing breast cancer by age 30, 40, and 50 is estimated to be approximately 2%, 10%, and 36% versus 4%, 20%, and 61% for BRCA1 alleles one and two, respectively.

The second of these studies is unique in that it incorporates information on a number of epidemiologic and genetic variables (19,32). This model, which estimates the probability that a woman with a given age and risk factors will develop breast cancer over a specified interval, was developed using data from the Breast Cancer Detection Demonstration Project (BCDDP). Risk estimates based on a variant of this model are being used to determine whether women under age 60 have high enough risk to be eligible to enroll in a national study of tamoxifen and breast cancer (34). In this model, relative risks are obtained from an unconditional logistic regression that includes age at menopause (AGEMEN), number of previous breast biopsies (NBIOPS), age at first livebirth (AGEFLB), number of mothers and sisters affected with breast cancer (NUMREL), age (less than 50 or greater than 50 years) (AGECAT), as well as two interaction terms, age by number of previous breast biopsies, and age at first livebirth by number of first-degree relatives affected with breast cancer. The model (referred to hereafter as the BCCDP model) expresses the log of the odds of breast cancer in the case-control population as:

$$\begin{aligned} \text{LOG ODDS} = & -0.74948 + 0.09401 (\text{AGEMEN}) + 0.52926 \\ & (\text{NBIOPS}) + 0.21863 (\text{AGEFLB}) + 0.95830 (\text{NUMREL}) + \\ & 0.0108 (\text{AGECAT}) - 0.28804 (\text{NBIOPS} \times \text{AGECAT}) - \\ & 0.19081 (\text{AGEFLB} \times \text{NUMREL}). \end{aligned}$$

Odds ratios can be computed from this equation. Using methods for combining such odds ratios with information on baseline hazards and competing risks (19), one can calculate the absolute risk of breast cancer over a defined time interval. Benichou (35) has written a computer program, RISK, which carries out these calculations and provides confidence intervals for the estimates. The following estimates were obtained from RISK, under the assumption that the only risk factors present concerned family history. The absolute risks of developing breast cancer by ages 30, 40, and 50 for a woman with a single first-degree relative are estimated to be 0.1%, 1.3%, and 4.4%, respectively (Gail M: personal communication), estimates that are similar to those calculated under the CASH model (27). For a woman with two first-degree relatives affected with breast cancer, the absolute risk of developing breast cancer by the age of 30, 40, and 50 is calculated to be 0.3%, 3.4%, and 11.1%, respectively. These risks are similar to those calculated under the CASH model for women with two first-degree relatives, both of whom had their breast cancers diagnosed in their 40s or 50s, and intermediate between CASH risks for women with two first-degree relatives affected in their 30s and women with two first-degree relatives affected in their 70s. The details of the BCCDP analyses as well as extensive relative risk tables for women with various combinations of risk factors are presented elsewhere (19,32).

The question remains then as to which risk tables should be used for the purposes of counseling young women with family histories of breast cancer. In the very near future, genetic screening tests will likely identify carriers of the BRCA1 breast susceptibility gene. For these women, it is appropriate to use the probabilities obtained from the Breast Cancer Consortium model. The numbers presented here should be interpreted as interim estimates; future population-based estimates of BRCA1 mutations will be obtained once the gene has been cloned (1). The extremely high risks predicted for these women indicate that this is a group who needs to be closely monitored; the ideal medical and/or surgical regimen for these women, however, is still being developed (36,37).

Current estimates of the gene frequency from the Consortium and additional analyses indicate, however, that the BRCA1 gene is likely to account for approximately 5%-7% of all breast cancers (1,37, and Claus EB, Schildkraut JM, Thompson WD, et al: manuscript submitted for publication). If this is true, then the majority of women with a positive family history of breast cancer will not carry a copy of this gene. In fact, among the families in the Consortium study characterized by breast cancer alone, there was little evidence of linkage to BRCA1 when the family contained fewer than four reported cases of breast cancer. For women with a positive family history who are noncarriers or unknown carriers, the tables provided by either the CASH or BCCDP models are likely to be of use. The tables, using data from the CASH study, are similar in format to those constructed by Ottman et al. (9) and by Anderson et al. (20). They differ from the tables of these two studies in that in the CASH data, a woman's risk is calculated conditional on the number and ages at onset of up to two affected relatives rather than by age at onset and bilaterality status of a single first-degree relative (9) or by laterality status of an affected sister and type of family his-

tory (20). In addition, the CASH tables are generated, using the estimated parameters of the most likely segregation analysis, rather than calculated from empirical risks as was done by the other two. The CASH analyses are strengthened by the fact that they are performed on a large, population-based data set, including over five times as many breast cancer cases as those in the previous studies (9,20). It should be noted, however, that even within a data set of this size, the number of women with multiple first-degree relatives affected with breast cancer at an early age is small; the error associated with estimates for this group of women is relatively large.

The BCCDP model is also quite useful in predicting the absolute risk of breast cancer. This model was initially constructed, using a slightly different data set than was the CASH model, i.e., using the BCCDP data. It is, therefore, most likely to be appropriate when used to counsel women who plan to be examined once a year, a group that should include women with positive family histories of breast cancer. Overall, if one uses only information on the number of affected first-degree relatives and assumes that no other risk factors are present, the estimates obtained from the BCCDP model for young women with family histories are fairly consistent with those from the CASH model. Any differences between the two models are likely to be due to a variety of reasons, including the nature of the data sets from which each model was constructed and from the fact that the CASH model includes information on the ages of onset of affected relatives, while the BCCDP model allows one to include the effect of additional variables, such as the effect of a benign breast biopsy on a woman's risk of subsequently developing breast cancer. For example, under the BCCDP model, the absolute risk of developing breast cancer by age 30, 40, and 50 years for a woman with a history of one benign breast biopsy and one first-degree relative affected with breast cancer is calculated to be 0.2%, 2.2%, and 7.4%, respectively. In general, the estimates calculated under the BCCDP model are somewhat higher than those calculated under the CASH model; the authors of the BCCDP model have found that the differences are likely to be due to the effect of screening (32) and indicate that their model is most appropriate when applied to a population undergoing yearly screening.

As information relating to both the genetic and environmental components of breast cancer increases, these risk tables will be revised. One must also consider the extent to which a woman's family history of ovarian (38) and additional (39) cancers affects the calculation of her risk of breast cancer. Linkage and epidemiologic studies indicate that approximately 10% of all ovarian cancer cases are carriers of the breast/ovarian cancer susceptibility allele (Claus EB, Schildkraut JM, Thompson WD, et al; manuscript submitted for publication). These individuals may thus confer an increased risk of breast cancer on their relatives. In addition, it appears that the presence of breast cancer in some families is not solely explained by the single autosomal dominant allele, BRCA1, and that additional genes (autosomal dominant or otherwise) will be found that influence a woman's probability of becoming affected with breast cancer (40). Other genes have already been implicated in the development of breast cancer, including the p53 gene located on the short arm of chromosome 17 (41) as well as rare alleles of a minisatellite ad-

jacent to the HRAS 1 gene located on chromosome 11 (42); the effect of these genes at a population level, however, is still unknown. In addition, individuals with other disease genotypes may be at increased risk of breast cancer as are those patients who are carriers of the ataxia-telangiectasia gene (43). Researchers have already examined and continue to examine other genomic regions and putative oncogenes. Therefore, future risk tables will include the effects of these genetic parameters. At present, however, with the exception of those women who carry the BRCA1 gene, young women with family histories of breast cancer must rely heavily on the extent to which their family members are affected with breast cancer to predict risk and to construct a health management plan. It is hoped that the information provided in this review may serve as a source of information for those women.

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Notes

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Screening Younger Women at Risk for Breast Cancer

Victor G. Vogel*

In women older than 50 years, screening mammography offers the benefits of decreased mortality from breast cancer, increased use of conservative surgery, and the reassurance of being free of breast cancer after a negative examination. No similar data are available for younger women. The cost to avert a single death from breast cancer in younger women may be \$2 million or more. One proposed strategy to improve the performance of screening mammography in younger women and to lower its cost is to restrict its use to women with risk factors for breast cancer, but this strategy will miss cases occurring in women who have no identifiable breast cancer risk factors. Because mammographic screening performance is different in younger women compared with older women, individual screening prescriptions based on risk may be appropriate until definitive trials demonstrate a mortality benefit in younger women. Additional research is needed to define the optimal screening strategy for both the entire population of women younger than 50 and those who are at increased risk for breast cancer. [Monogr Natl Cancer Inst 16:55-60, 1994]

Breast cancer remains an important public health problem in the United States, and more than 183 000 new cases will be diagnosed in 1993 (1). Incidence rates rose approximately 4% per year during the years 1982 to 1986 (2,3). While the majority of new cases of breast cancer occur in women aged 50 years and older (2), the psychologic impact and social consequences of the disease in younger women can be profound (4).

It is now well established that screening mammography can reduce mortality from breast cancer by 30% or more in women older than 50 years (5). It is difficult, however, to find data that support mortality reduction through mammographic screening for women younger than 50 years. This manuscript will review the available data and examine both the benefits and risks of screening younger women with mammography. The limitations in the data concerning mammographic screening in younger women will be discussed along with the possibility of a selective screening strategy based on risk factors. The problems associated with risk assessment and selective screening will be reviewed, and recommendations for additional research on screening mammography in younger women will be proposed.

Available Data on Screening Mammography

Mammographic screening offers several benefits as well as risks. Among the benefits are a demonstrated decrease in mor-

talidity for women older than 50 years, the ability to use conservative surgery for smaller, less advanced lesions, and the psychologic reassurance gained by a woman after a negative mammogram (5). These benefits are accompanied by physical discomfort as a result of the compression techniques used for state-of-the-art mammography, and screening increases the possibility of women having to undergo additional investigations, including breast ultrasound, fine-needle aspiration, needle biopsy, and open biopsy. In addition, there is the possibility of overtreating lesions that are actually benign clinically and that would not have come to clinical attention in the absence of screening. Unnecessary surgery and radiation therapy may be used to treat these lesions that impose no threat to health.

Screening mammography has inherent limitations in its sensitivity, and as many as 15% of negative mammograms may be false negative (6). The false reassurance that follows a negative mammogram may lead to decreased compliance with attendance at future scheduled screenings. There is also some psychologic morbidity associated with undergoing mammographic screening. Published studies show that some women experience an increase in measured anxiety and psychologic distress immediately following mammographic screening (7,8).

Mammographic screening detects breast lesions that may not otherwise come to clinical attention. Lantz et al. (9), examining breast cancer incidence in Wisconsin for the years 1982 through 1988, showed that 60% of the apparent increase in breast cancer incidence among women aged 40-49 years was due to an apparent increase resulting from screening. This increase was largely attributed to a 328% increase in in situ cancers and a 37% increase in localized cancers. Detection of these early, clinically nonthreatening lesions is a challenge for the clinician because it is not always clear which lesions should be treated with radiation and/or chemotherapy and which can be treated by excision only. This dilemma also plays a role in the psychologic morbidity among women screened, because of the uncertainty that surrounds optimal clinical management of early lesions.

Because of all these potentially adverse effects, it is important to re-examine the recommendation for screening mammography every 12-24 months in women 40-49 years of age.

Table 1 lists the completed randomized, prospective mammographic screening studies reported in the medical literature.

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See "Notes" section following "References."

The earliest of these, the Health Insurance Plan of New York (10), began in 1963, and the last to be completed, the Stockholm study, began in 1981 (11). Mammographic screening techniques have changed dramatically in the 30 years since the Health Insurance Plan study began in 1963. Consequently, the generalizability of the earlier results must be questioned. In addition, only three of the studies listed in Table 1 incorporated today's standard two-view mammography. The screening interval for women in these trials was usually 24 months or longer, and only two of the trials used a 12-month screening interval. These historical features and limitations of the completed studies make it very difficult to generalize the findings to the current use of mammographic techniques or appropriate screening intervals.

With the exception of a prospective trial done in Canada (12), none of the published studies was designed specifically to address the question of a reduction of breast cancer mortality in women under the age of 50 years. Data about younger women can only be derived from subset analyses of the screened populations in the published studies. Table 2 shows the number of women under 50 years of age in each of the published studies, along with the number of years of follow-up and the observed changes in breast cancer mortality when women in the mammographic screening group are compared to the women in the control group in each study. This ratio is expressed as the

relative risk of dying from breast cancer along with 95% confidence intervals in the last column of the table. These same data are shown graphically in Fig. 1. A reduction in breast cancer mortality was seen in only three of the published studies, and all of the 95% confidence intervals around these estimates of mortality reduction included 1.0. Therefore, none of these studies offers convincing evidence that mammographic screening of women aged 50 years or younger reduces mortality from breast cancer.

Unfortunately, the published studies do not resolve the issue of whether mammographic screening is of benefit to women younger than 50 years of age. The first reason is that none of these studies, with the exception of the Canadian National Breast Screening Study (NBSS) (12), has sufficient power to demonstrate mortality reduction in younger women because the studies were not designed with that purpose in mind. Even though the Canadian study was so designed, a number of problems handicapped the conclusions derived by the investigator.

The problems with the NBSS can be summarized as follows (13): 1) Women with palpable breast masses were not excluded from the trial, and a greater number of patients with advanced cancer were allocated by chance to the group that received screening mammography. This made the demonstration of a mortality benefit very unlikely because of this unintended randomization bias. 2) There were significant problems with the quality of the screening mammography as evidenced by the fact that, unlike other published screening studies in older women, the Canadian study did not show lower mortality in women older than 50 years (14). In addition, external review of the mammograms done in the first 4 years of the trial showed that 50% were poor or of completely unacceptable quality. This may have occurred because there was no special training for the technologists or the radiologists involved in the study. 3) Internal review of the screening mammograms by the reference radiologist for NBSS showed that the quality of mammographic interpretation was deficient: 42% (43 of 102) of the interval cancers were seen on retrospective review of the study's mammograms, and 17% (100 of 575) of breast cancer cases detected at screening were found on review of prior mammograms taken in the project 2-5 years before the project radiologist declared a mammographic abnormality was present. 4) Biopsy of mammographically detectable lesions was not performed in 25% of the cases for whom it was recommended. Therefore, NBSS does not resolve the question of whether mammographic screening in younger women lowers mortality from breast cancer.

Using the data from the studies cited in Tables 1 and 2, Eddy et al. (15) calculated the theoretical benefits of 10 years of annual mammographic screening in women aged 40-49 years. Based on the published detection rates and mortality reductions, 22 deaths could be averted for every 10 000 women screened with annual mammography between the ages of 40 and 49. The cost of averting one death was \$2 million 1984 dollars. The authors suggested that a selective screening strategy concentrating only on women at increased risk could reduce deaths from breast cancer by a factor equal to the relative risk of breast cancer in the women screened. In addition, cost would be reduced proportionally to the relative risk of those screened. For ex-

Table 1. Techniques and follow-up intervals in randomized mammographic screening trials

Study	Ref. Nos.	Year started	Mammography	
			Views	Interval, mo
Health Insurance Plan	(10)	1963	2	12
Malmö	(24)	1976	2	18-24
Swedish 2-counties	(25,26)	1977	1	24
Edinburgh	(27,28)	1979	1	24
Canadian	(12,14)	1980	2	12
Stockholm	(11,29)	1981	1	28

Table 2. Mortality reduction attributable to mammographic screening among young women younger than 50 years in randomized trials*

Study	No. of women <50 y old at entry	Years of follow-up	Relative risk
			(95% confidence interval) of dying of breast cancer, screened versus control
Health Insurance Plan	9323	5	0.95 (0.51-1.78)
		10	0.77 (0.50-1.16)
		18	0.75 (0.52-1.09)
Swedish 2-counties	19 937	6	1.26 (0.56-2.84)
		8	0.92 (0.52-1.60)
		11	1.03 (0.65-1.63)
Malmö (<55 y)	7981	8.8	1.29 (0.74-2.25)
		11	1.08 (0.65-1.79)
Canadian	50 430	8.5	1.36 (0.84-2.21)
Edinburgh	5913	7	0.98 (0.45-2.11)
Stockholm	14 375	7	1.09 (0.40-3.00)

*Modified with permission from Hurley SF, Kaldor JM. *Epidemiol Rev* 14:101-130, 1992.

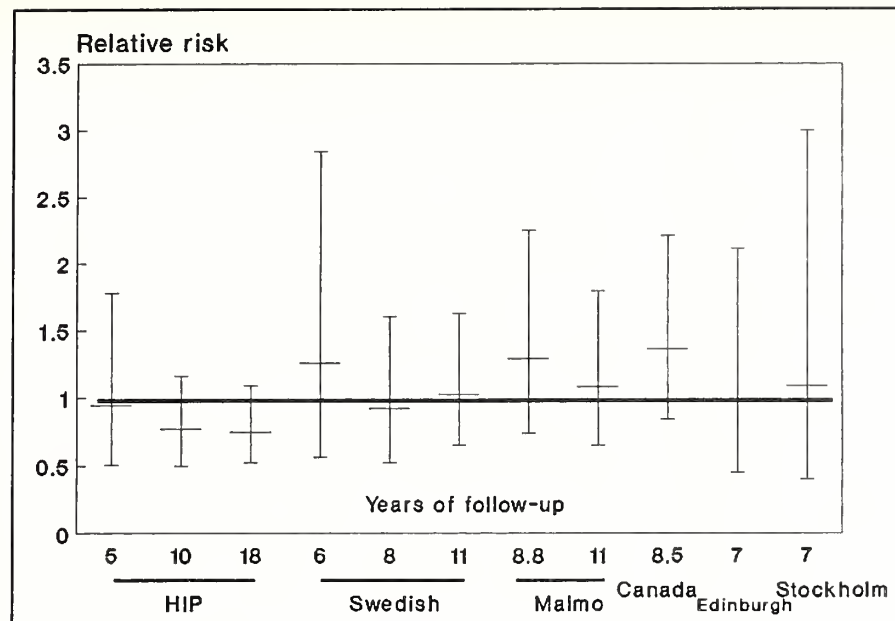


Fig. 1. Relative risk of dying of breast cancer in six prospective, randomized mammography screening trials. A relative risk of 1.0 indicates no benefit, while relative risks <1 indicate reduction in mortality and risk >1, an increase in mortality. Bars show point estimates of the risks at different lengths of follow-up and 95% confidence intervals of the estimates. Data are derived from Table 2.

ample, if a group of women at threefold risk could be identified, 66 deaths (22×3) could be averted for every 10 000 women screened at a cost of \$668 000 (2 million/3) per death averted. Similarly, if women at fivefold increased risk could be identified, the cost would be \$400 000 per death averted among each 10 000 women screened. Eddy et al. (15) concluded that a recommendation for screening in younger women should recognize both the overall mortality reduction and the cost of achieving such a reduction. They suggested that individual screening prescriptions may be appropriate for patients after consultation with a physician, but they did not address the difficulties or costs associated with identifying a group of women who are at increased risk for breast cancer or the need for informed consent if selective screening is promoted (16). Before addressing the issue of selective screening, it is necessary to estimate the magnitude of the breast cancer problem in younger women and the theoretical benefits potentially available through mammographic screening.

Screening Younger Women

If mammographic screening of women under the age of 50 years reduces mortality by the same degree as it does in older women, substantial benefits would accrue to the population of the United States. Table 3 lists the 1990 U.S. population for whites and blacks (in thousands) and the corresponding breast cancer incidence rates by race for women in 5-year age groups from 30 through 49 years. The number of incident cases of breast cancer by age for whites and blacks is also shown in the table. More than 32 000 incident cases of breast cancer occur annually in the United States among these two racial/ethnic groups. In women whose breast cancer is not detected by screening, half will die of complications from breast cancer. In women older than 50, screening mammography reduces breast cancer mortality by 30% (5). If screening in younger women were to reduce mortality from breast cancer by the same proportion, the application of screening mammography to this popula-

tion of younger women would prevent more than 4800 deaths from breast cancer. This theoretical reduction in mortality would be achieved only after screening more than 33 million women annually for 10 years if mammographic screening in younger women is as effective as in older women. This benefit has not been demonstrated.

The cost of screening the entire population of younger women would be substantial, and patients must be made aware that they ultimately pay for mammographic screening whether they are insured, taxed, or pay costs out-of-pocket. If one attempts to contain costs by screening only those with risk factors, we cannot be certain that sufficient numbers of women with risk factors for breast cancer can be identified. The National Health Interview Survey (Table 4) showed that less than 8% of women in the population under the age of 49 years have relatives affected with breast cancer (17). When present, this risk factor may increase the risk of breast cancer severalfold. Nulliparity and early age at menarche, two other important risk factors, are

Table 3. Theoretical number of deaths averted by mammographic screening in women 30-49 years old*

Age group, y	(1) 1990 Population (thousands)†		(3) Incidence (per 100 000)‡		(5) No. of incident cases		(7) No. of deaths averted
	White	Black	White	Black	White	Black	
30-34	8652	1431	26.1	34.2	2258	489	412
35-39	8027	1254	65.2	79.9	5234	1002	935
40-44	7279	1010	129.7	141.5	8441	1429	1631
45-49	5849	763	190.8	173.6	11 160	1325	1873
Total	29 807	4458			28 093	4245	4851
					(a)	(b)	(c)

* (a) = col (1) \times col (3); (b) = col (2) \times col (4); (c) = 30% reduction in mortality from breast cancer among whites and blacks, assuming 50% of unscreened patients die: $1/2 \times [\text{col (5)} + \text{col (6)}] \times 0.30$.

† From U.S. Bureau of the Census (30).

‡ From NCI SEER data, 1973-1988 (2).

seen in 16% or fewer of the female population of the United States. The magnitude of the relative risk associated with risk factors, such as a family history of the disease in first-degree relatives, can be substantial (i.e., greater than fivefold excess risk), but most other identified risk factors have associated relative risks less than 2. While other risk factors for breast cancer may be used to identify those at increased risk, it is likely that no more than 20% of the population is at substantially increased risk of the disease due to attributable risk factors (18).

Recognizing that it may be difficult to identify significant numbers of younger women having risk factor profiles that place them at substantial increased risk, it is possible to make theoretical calculations about the benefit of screening of women with risk factors for breast cancer other than age. Risk factor profiles can be described that increase the risk of breast cancer at least threefold in 20% of women in the United States between the ages of 30 and 49 years. Table 5 shows an estimate of the number of incident cases of breast cancer occurring in both white and black U.S. females who are at increased risk for breast cancer. These numbers were derived by multiplying the

incidence figures for each racial/ethnic group shown in Table 3 by 3 and then applying these higher incidence rates to 20% of the respective populations by age. The number of incident cases in women at usual risk was then obtained by subtracting the number of incident cases occurring in women at increased risk in Table 5 from the number of incident cases by race listed in Table 3. The calculation equations are listed in the footnotes to Table 5.

An additional assumption for Table 5 is that only the women at increased risk would be screened with annual mammography. With this strategy, an estimated 2910 deaths from breast cancer could be averted if screening mammography was performed only in women at increased risk. This would be accomplished at the expense of missing the opportunity to detect nearly 13 000 incident cases of breast cancer occurring annually in women at usual risk. If the same assumptions apply to women at usual risk as to those at increased risk, more than 1900 breast cancer deaths could be averted through annual screening in women at usual risk for breast cancer. It is, therefore, difficult to argue that screening should be done only for those at increased risk, even though one prospective validation study indicates that application of published multivariate risk cancer models (19) can predict breast cancer incidence accurately in the short term (20). Additional validation studies will be required, however, before reliable selective screening strategies can be employed.

Discussion and Directions for Future Research

Screening mammography may offer reduced mortality from breast cancer for women under 50 years of age, but available published data do not yet support such a view. Sensitivity and specificity of screening mammography in younger women are not well defined (6) and there are clinical limitations on the performance of screening mammography in younger women that may limit its performance as compared to older women. Despite its intuitive appeal, a selective screening strategy using risk factors to select candidates for annual screening would miss a substantial number of breast cancers in younger women. No published study has shown a benefit in mortality reduction from a selective screening strategy in women at increased risk. None of the completed mammographic screening studies has either sufficient methodologic rigor or significant power to prove that screening is beneficial (or detrimental) in women younger than 50 years.

Despite these limitations, a recent update and overview of the experience of the Swedish randomized screening trials show a nonsignificant 13% reduction rate in mortality among women aged 40–49 years at entry that did not appear until the follow-up interval had exceeded 8 years (21). This suggests that inadequate observation intervals may be responsible for a lack of benefit in the published trials. Other overview analyses cite additional reasons for the lack of benefit in younger women, including biological differences in premenopausal (as compared to postmenopausal) breast cancer, differences in risk factors in younger women, differences in tumor characteristics and responsiveness to chemotherapy, and differences in breast density in younger versus older women (22). The lack of conclusive

Table 4. Distribution of breast cancer risk factors in the United States, 1987*

Risk factor	%
Have a relative with breast cancer	
Women aged 40 y and over	
1 primary relative (mother, sister, daughter)	7.9
Mother	4.0
Sister	3.7
Women aged 40–44 y	
Mother	4.0
Sister	1.4
Women aged 45–49 y	
Mother	5.6
Sister	4.0
Parity among ≥40 y	
Nulliparity	14.2
Age at first live birth 30 y or older	7.1
Age at menarche <12 y among women ≥40 y	16.0

*From National Health Interview Survey (17).

Table 5. Number of deaths averted by mammographic screening if 20% of women are at threefold increased risk and only they are screened*

Age group, y	(1) Incident cases among women at increased risk		(3) Incident cases among women at average risk		(5) No. of deaths averted by screening
	White	Black	White	Black	
30–34	1355	294	903	195	247
35–39	3140	601	2094	401	561
40–44	5665	857	3776	572	978
45–49	6696	795	4464	530	1124
Total	16 856	2547	11 237	1698	2910
	(a)	(b)	(c)	(d)	(e)

*Data were derived from the sources cited in Table 3. Incidence rates among women at increased risk are assumed to be three times the age- and race-specific incidence rates shown in Table 3. (a) = [Table 3, col (1) × 0.20] × [Table 3, col (3) × 3]; (b) = [Table 3, col (2) × 0.20] × [Table 3, col (4) × 3]; (c) = [Table 3, col (5)] – [Table 5, col (1)]; (d) = [Table 3, col (6)] – [Table 5, col (2)]; (e) = 30% reduction in mortality from breast cancer among whites and blacks, assuming 50% of unscreened patients die: $1/2 \times [\text{col (1)} + \text{col (2)}] \times 0.30$.

data about these differences indicates the need for additional research.

There are both potential benefits and risks from screening younger women with annual or less frequent mammography. With the increasing emphasis on containment of rising health care costs, an important reality of mammographic screening in younger women is that it may require that they forego other health care services, some of which may be of greater demonstrated benefit than screening mammography in younger women (23). Only limited data are available to assess relative costs and benefits of screening younger women. Estimates of cost-benefit ratios are dependent on the technology employed when the data were derived. For example, if data from the Health Insurance Plan study that began in 1963 are used, the cost per year of life saved for women aged 40-50 years is \$134 000 (22), but this cost falls to \$29 000 using data from the Breast Cancer Detection and Demonstration Project 10 years later. Additional revisions of the cost estimates will be required, using mortality data for younger women from screening studies in progress.

Carefully designed, prospective studies of screening mammography in younger women are urgently needed, but these studies must grapple with the impression left in the minds of the public and the medical community that screening younger women is already known to be beneficial. Therefore, such studies may be impossible to design with observational control groups who do not receive mammographic screening. A study that is feasible is a comparison of different screening intervals in a population of women aged 40-49 years at increased risk. The base-line breast cancer incidence in women at usual risk in this age group is approximately 1.5 cases per 1000 women per year (Table 3). Women at threefold increased risk can be identified in the population whose incidence is then four to five cases per 1000 women per year. At least half these women will die of breast cancer if their breast cancer is detected clinically. A randomized trial comparing annual screening to screening every 24 months should be conducted in these women. Assuming a 30% mortality reduction with annual screening compared to the longer interval, nearly 59 000 women would be required in each of two groups to show this difference with 80% power at a significance level of .05. Such a trial may be too costly to be feasible.

Creative alternative design strategies must be employed. A careful evaluation of the sensitivity, specificity, and predictive value of screening mammography in younger women is needed, along with a careful evaluation of the specific techniques that may be uniquely appropriate for this population of women. Finally, a prospective evaluation of a selective screening strategy that is targeted at women who are at increased risk of breast cancer should be developed, because an increasing number of these women are receiving regular screening in the absence of demonstrated and proven benefit. All of these questions offer significant opportunity to increase our knowledge about breast cancer detection in younger women along with an opportunity to reduce mortality from this very important public health problem. Until new research is completed, compliance with the recommended screening guidelines should continue. Both physicians and patients should recognize that the potential

benefits of screening are substantial, while also understanding the possibility for harm, however small.

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Prevention of Breast Cancer in Premenopausal Women

Richard R. Love*

While all-inclusive complete models for breast cancer development are not available, four concepts are likely to be critical to creation of well-grounded breast cancer prevention efforts: 1) step-by-step progressive development, 2) involving multiple factors, 3) over several years, and 4) during a long period of which the process may be reversible. Interventions to prevent breast cancer must have a comprehensive biological rationale, an absence of serious toxic effects, and long-term acceptability by women. Prophylactic mastectomy may be beneficial in some women, but identification of individuals at very high risk for breast cancer remains elusive. At present, greater attention to four manipulable risk factors is appropriate: radiation, smoking, alcohol, and lactation. Clinical trials are in the process of studying a synthetic retinoid (4-hydroxyphenylretinamide), tamoxifen, and a low-fat diet. Other breast cancer prevention strategies in various phases of preclinical trial evaluation include: pseudopregnancy, an "ideal" combination oral contraceptive, luteinizing hormone-releasing hormone (LHRH) agonist oophorectomy, modification of estrogen metabolism, suppression of ornithine decarboxylase induction, and manipulation of growth factors. [Monogr Natl Cancer Inst 16:61-65, 1994]

The ideal basis for design of interventions to prevent breast cancer is a comprehensive model for the development of this malignancy. While there are many epidemiologic data on breast cancer, to many investigators these appear fragmented because they don't all fit together in rational models of disease development. For example, while it is clear that changes associated with ovarian function—age at menarche or at first full-term pregnancy—are important, which hormones are most important and particularly what effects progestogens have on the breast are unknown. Additionally, it is unsettling that many breast cancers occur in women without attributable risk factors (1). Nevertheless, some framework for breast cancer development can be suggested (Fig. 1). The layout of the words about steps or stages in this table embodies some key and evolving concepts from cancer biology. First, cancer development is characterized by step-by-step progression. While a working model of hypothesized molecular steps in breast cancer is not yet available, the development of data-supported models for colorectal cancer suggests that this principle will also apply to breast cancer (2). Second, cancers develop over many years; for breast cancer, this principle is well supported by data indicating a lag in develop-

ment of invasive disease of 10-15 years after radiation exposure (3). Third, the two-way arrows during a presumed lengthy promotion or modification phase signify reversibility of the process. This concept is not yet well-supported for breast cancer but is a fundamental one that is assumed to be operative in this malignancy. Finally, in this table the multiplicity of mechanistic factors listed, without suggested sequential or different developmental pathways (other than the implication that the first three factors on the left precede the others as actors in the process), emphasizes the concept that our current knowledge is that multiple factors usually play important roles.

In other papers in this monograph, specific data supporting the consideration of these categories of mechanistic factors in breast cancer are provided, and here in the context of consideration of interventions based on these groups, they will be reviewed in limited ways. Some overall framework for breast cancer development must set the stage for discussion of preventive interventions or our intervention efforts may appear less related to basic biology than they really are.

From Theory to Successful Application

Absence of complete, all-inclusive models notwithstanding, several rational interventions to prevent breast cancer can be implemented, are in clinical trials, or are being actively explored in preclinical trial studies. There are major differences between the

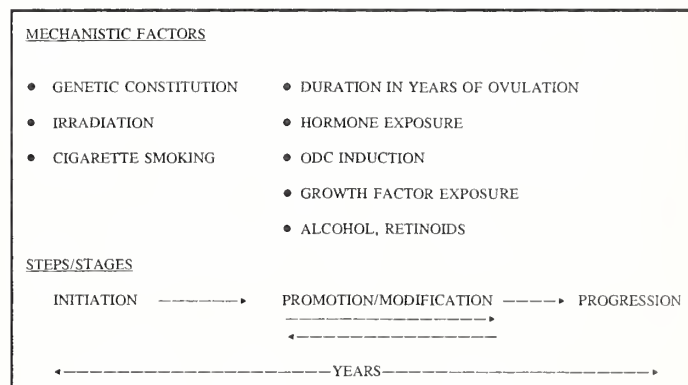


Fig. 1. Mechanistic factors and stages in development of breast cancer.

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See "Note" section following "References."

preapplication-in-humans process necessary for preventive interventions and that for therapeutic interventions. In treating cancer, we usually are dealing with circumstances where lack of success means that the afflicted individuals will die. In such situations, when no viable alternatives are available, we are often willing to act on an incomplete biological rationale, and accept serious, occasionally life-threatening toxicity. The patients themselves are willing to accept often noxious treatment.

With prevention, however, there are no "patients," only healthy people who are at risk for breast cancer as a group, but for whom individual risk cannot be defined precisely. In these circumstances, for interventions to become useful to populations, the process of evaluation must result in: 1) a comprehensive biological rationale for the intervention; 2) demonstrated absence of serious toxic effects on organs, tissues, and risk factors for diseases; and 3) demonstrated long-term acceptability to healthy populations. These criteria provide a useful framework for discussing current breast cancer preventive interventions.

It is worthwhile to consider briefly the reasons why these criteria are proposed. First, a comprehensive biological rationale and all toxicity data are necessary, because in a healthy population only a minority of subjects will develop breast cancer; therefore, if the intervention has any adverse biologic effects these will occur in many people who don't need any "treatment." If an intervention has only a single biologic reason for its use and other possible biologic effects are not understood or have not been investigated, this is inadequate. Two examples may better illustrate why comprehensive data are necessary. Cigarette smoking has been suggested to affect ovarian function in a manner that might decrease breast cancer risk (4). This may be, in fact, why smoking has not been linked to breast cancer development, despite plausible arguments that this should be the case (5). While obviously no one would propose cigarette smoking as a preventive intervention, this offers an extreme example of how just looking at one biologic effect and acting on it could be disastrous. A second component suggested by this example that is important is that the toxic effects data must be comprehensive in considering all consequences of the intervention on all organ systems. Obviously, cigarette smoking has hazardous effects on tissues other than the breast. This suggests that an ideal intervention should be quite breast cancer "specific"—a significant demand. A second example, more germane to current research activities, concerns evaluation of tamoxifen as a chemosuppressive agent in both premenopausal and postmenopausal women in an ongoing National Surgical Adjuvant Breast and Bowel Project trial. While the biological rationale and toxicity profile for this intervention in postmenopausal women is well developed for both breast and other organ/tissue effects, the same cannot at all be said for premenopausal women (6). In premenopausal women, major hormonal perturbations occur with tamoxifen that do not occur in postmenopausal women (6,7), and these can be expected to modify or reverse the direct tissue-specific actions of tamoxifen seen in postmenopausal women.

Long-term acceptability of an intervention is also an essential criterion, because for most interventions long-term application

is necessary. This seems obvious and is easy to say, but the predictors of long-term acceptability and therefore compliance make obvious that this criterion is often painfully challenging to satisfy. Populations cannot be benefitted by an intervention they won't take, and when fully informed of potential risks and toxic effects, large fractions of populations may be expected to express no interest at all in, or to comply only temporarily with, preventive interventions.

Currently Implementable Interventions to Prevent Premenopausal Breast Cancer

Currently implementable interventions to prevent premenopausal breast cancer are as follows: avoidance of breast irradiation (particularly in adolescents); avoidance of cigarette smoking (particularly in adolescents), avoidance of alcohol, encouraging long-duration lactation, and prophylactic mastectomy.

Long-term real increases in the incidence of breast cancer in premenopausal women suggest that alterable risk factors must be operating in the development of this disease (8). While changes in reproductive practices, specifically later age at full first-term pregnancy or frequency of nulliparity, may offer some explanation, other factors, which may be more practically altered, appear to be operating also (9).

The strongest evidence for a modifiable initiating factor in premenopausal breast cancer is that for irradiation (3). A recent report on the occurrence of breast cancer following radiation for Hodgkin's disease has again emphasized the profound effect of this factor in younger women (10). These data prompt efforts at more careful consideration of ways to limit breast irradiation as part of therapeutic treatment programs. A greater difficulty is in knowing how much to be concerned about low-dose diagnostic radiation exposures, particularly for possibly higher risk, but not easily or presently identifiable populations. Questions are prompted because of observations regarding individuals who are heterozygous for the ataxia telangiectasia (AT) gene.

In brief, AT heterozygotes are suggested to account for 9%-18% of breast cancer subjects, while representing 1.4% of the population (11,12). Are these individuals and others heterozygous for familial and chromosomal breakage syndromes high risk for low-dose radiation populations for whom special measures are warranted? As a general proposition, these considerations urge even more careful consideration of benefits in use of diagnostic radiation, particularly in women under age 20.

While the breadth of evidence for cigarette smoking, active or passive as a cause of breast cancer is not wide, the magnitude of the data from Hirayama (13) cannot be ignored and the hypothesis is rational (5). Data implicating alcohol as an etiologic factor in breast cancer continue to be reported (14). Prolonged duration of lactation is also of increasing interest as a protective factor against premenopausal breast cancer (15). While the mechanism of this effect is not yet clarified, this behavior should probably be more encouraged than it has been in the past.

For each of these four interventions, consideration of the biological rationale and toxic effects reveals no persuasive case against their implementation. For each, however, acceptability and applicability for included women will depend on cir-

cumstances. For prophylactic mastectomy, however, the issue of acceptability is obviously paramount. If one achieves removal of all breast tissue (which cannot occur, even with breast cancer surgery), then intuitively it seems reasonable to expect that risk of invasive breast cancer is reduced to negligible levels. It must be acknowledged, however, that good evidence for such benefit is lacking. Even if one accepts that benefit is likely, as a strategy prophylactic mastectomy continues to have an uncertain role, because at present it is difficult to quantify precisely the risk an individual woman has and thus the extent of the possible benefit cannot be posited.

In summary, although our information falls short of comprehensive and only special populations can be targeted and benefitted, with the exception of mastectomy, these are currently nonharmful interventions that should be more widely implemented with a reasonable expectation that breast cancer prevention will result.

Premenopausal Breast Cancer Interventions Being Evaluated in Clinical Trials

At present, three interventions are being tested in randomized clinical trials: 4-hydroxyphenylretinamide (4-HPR), tamoxifen, and a low-fat diet. Retinoids appear to act as antiproliferative, and in some circumstances differentiating, agents. Based on these major beneficial biologic effects demonstrated *in vitro* and *in vivo* in animal systems, evaluation of one form, 4-HPR, is ongoing in an Italian study in which the development of a new second primary breast cancer is the major end point (16). The major challenges with retinoids concern their teratogenicity and hepatic and cutaneous toxic effects, and these are possibly serious barriers to widespread application.

Tamoxifen, a synthetic estrogen agonist antagonist is being evaluated in large primary prevention trials in the United States, the United Kingdom, and Italy. Concerns about the biological rationale and the incomplete toxicity profile for premenopausal women have been noted earlier. To extend these further, it is notable that in an *in vivo* system wherein an inoculation of MCF-7 cells (a widely used breast cancer cell line) is injected subcutaneously into the flank of a nude mouse, under conditions of low blood levels of tamoxifen and high blood levels of estradiol, tumor growth occurs (17). These conditions are observed in premenopausal women treated with tamoxifen (7). That these data might have clinical relevance is attested to by the observation that in premenopausal women second primary breast cancers were found to be *more* common in tamoxifen-treated women in the Cancer Research Campaign (CRC) adjuvant breast cancer trial, while the opposite was observed in postmenopausal women (18). As of early 1993, these were the only formally reported data about second primary cancers with tamoxifen in premenopausal women. The spectrum of questions about unknown effects of tamoxifen for premenopausal women in particular is as follows: impact on incidence of second primary breast cancer with adjuvant treatment; characteristics and treatability of "breakthrough" breast cancers occurring on tamoxifen treatment; incidence of uterine, colorectal, liver, and ovarian cancer; impact on cardiovascular disease risk factors, impact on risk factors for osteoporosis; impact on lens, retina,

and macula; impact on mood-incidence of depression; impact on incidence of thrombophlebitis and cholelithiasis; impact on immune function; and important drug interactions. Beyond the biologic and toxicity criteria, there are major questions about long-term acceptability of tamoxifen in premenopausal women.

While the biologic and ecologic rationales for investigating a low-fat diet as an intervention to prevent breast cancer have been lucidly explicated (19,20), corroborative epidemiologic data have been limited or absent (21). Given likely health benefits overall and the circumstance that only a rigorous intervention study can answer the question definitively, intervention trials are under way. The longest duration trial is in Canada, where with 3000 women-years on study, and continuing accrual, the as-yet unreported data indicate no reason to stop the study (Boyd N: personal communication, January 1993).

Premenopausal Breast Cancer Prevention Approaches in Preclinical Evaluation

Based on models and understanding of mechanistic factors important in breast cancer development, several approaches to breast cancer prevention are under study in laboratory and, in some cases, pilot human studies. For each of these, rigorous data on the comprehensive biologic effects on breast and other tissues are needed. These interventions include pseudopregnancy, an "ideal" combination oral contraceptive, luteinizing hormone-releasing hormone (LHRH)-agonist hormonal oophorectomy, modification of estrogen metabolism, ornithine decarboxylase inhibition, and growth factor control.

Pseudopregnancy

Pregnancy, particularly full-term pregnancy early in life, lessens the risk for subsequent invasive breast cancer (22). As a result of elegant laboratory experiments, Russo et al. (23) have suggested that pregnancy results in differentiation of terminal end bud breast cells, removing susceptible proliferating cells from possible influence by various carcinogens (radiation, for example). If this same effect could be achieved by a temporary hormonal intervention, causing "pseudopregnancy," risk of breast cancer should be significantly decreased. The timing of such an intervention and the optimal hormonal differentiation-producing combination are under intense investigation. The suggestion that certain oral contraceptives used in young women increase the risk of breast cancer and vascular events shows the hazards of defining a hormonal treatment with favorable biologic effects on all hormonally sensitive tissues and their products (24).

An "Ideal" Combination Oral Contraceptive

In considering similar data, particularly those suggesting that progestogens both increase cell proliferation in the estrogen-primed breast and cause terminal differentiation of proliferating cells, Stoll (25) has argued that formulation of an "ideal" oral contraceptive that reduces breast cancer risk should be possible. Since current data indicate reduced risk of endometrial and ovarian cancers associated with oral contraceptive use, such a formulation, if also having these effects, would be "ideal" (26).

The epidemiologic evidence suggesting that long duration of ovulation in years and the increasing length of the time from menarche to full first-term pregnancy are associated with increased risk of breast cancer have prompted the possibility of abolishing ovarian activity by administration of an LHRH agonist (27). To manage the significant estrogen-deficiency cardiovascular and skeletal adverse effects and the vasomotor and other symptoms, low-dose hormonal replacement therapy could be given (28). This general approach appears to have more appeal for older women, that is women in their 40s, because of the limited time they would need to take the treatment and because of uncertain consequences for fertility, and thus may be of less relevance in the prevention of premenopausal breast cancer.

Modification of Estrogen Metabolism

A variety of data suggests that strategies to modify estrogen metabolism may decrease risk of breast cancer. Increased physical activity (28) and avoidance of overnutrition, particularly in adolescence, may delay onset of menarche. These seem to be practical interventions deserving of careful study, but not without possible adverse effects. Pharmacologic interventions to alter hormone levels may be significantly protective and also deserve detailed study (29).

Ornithine Decarboxylase Inhibitors

Ornithine decarboxylase (ODC) is an enzyme that catalyzes the synthesis of the polyamine putrescine from ornithine. Polyamines appear to play a major role in growth regulation. ODC suppression appears to be an integral part of reversing tumor promotion. In animals, specific irreversible inhibitors of ODC, such as difluoromethylornithine (DFMO), are potent inhibitors of mammary tumor development (30). Given at a dose that exhibits no discernible toxicity in humans, DFMO has been shown to have a significant ODC induction-suppressing effect on the skin (31). Other ODC inhibitors, retinoids and non-steroidal anti-inflammatory drugs, may also have significant breast cancer prevention potential.

Growth Factor Control

Lippman et al. (32) have conducted a series of detailed studies investigating the molecular mechanisms important in breast cancer growth. These studies suggest various possible strategies through which very targeted and specific approaches to control breast cancer development may be achieved.

Summary

In the face of apparently increasing incidence of premenopausal breast cancer and frustratingly limited gains in treatment, significant possibilities for widespread prevention of breast cancer must be vigorously explored. In this approach, however, progress appears to be painfully slow, for which the multifactorial etiology of breast cancer development is most responsible. The challenges in our approaches are to recognize the major differences between treatment and prevention and to demand a comprehensive biological rationale, an absence of serious toxic

effects, and likely long-term acceptability to women of interventions coming to definitive clinical trial.

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Section IV: Treatment

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The impact of young age on treatment and outcome in women with breast cancer remains controversial. Two factors have contributed to this debate. The first is the lack of a consistent definition of young age. A number of series have identified the young premenopausal woman, i.e., less than 35-40 years of age, as having a diminished survival when compared with the older premenopausal woman, i.e., 40-49 years (1,2). However, in many studies, the division of the patient populations has been based on menopausal status, i.e., pre versus post or age ≤ 50 years versus > 50 years. This simple distinction serves to obscure the prognosis of the young woman. While the most appropriate definition of young age remains to be determined, it is most likely that its maximum upper limit should be 40 years. The second factor that contributes to conflicting results is the fact that less than 10% of all women with breast cancer are diagnosed at age 40 or less (3-7). Therefore, the relatively small number of young women with breast cancer results in limited data.

The clinical presentation of the young woman with early-stage breast cancer is significantly different from that of the older woman. Young women are less likely to be diagnosed solely on the basis of mammographic findings and are more likely to have histologically positive axillary nodes (3,8-10). In histopathologic reviews, younger women have been found to have a greater incidence of tumors with an extensive intraductal component (5,11-13), tumors that are of high histologic grade (5,8,9,14,15), have lymphatic or vascular invasion (9,12), or a major mononuclear cell reaction (5,12), and are more likely to be estrogen- and progesterone-receptor negative (3,10,16,17). The increased prevalence of these adverse pathologic factors in young women may be in part responsible for what appears to be a more biologically aggressive disease.

Treatment-related issues in the young woman with breast cancer include the timing of the surgical procedure with the menstrual cycle, the options of conservative surgery and radiation or mastectomy and reconstruction, the effect of adjuvant systemic chemotherapy and high-dose chemotherapy either in the adjuvant setting or for the treatment of metastatic disease, as well as the concept of ovarian ablation. An important question that remains to be answered is what is the effectiveness of our current treatment strategies in the young woman with breast cancer when compared with the older woman.

While the younger woman may more often choose breast-conservation therapy, an increased risk of breast recurrence following conservative surgery and radiation has been associated with young age (3,5,13,18-21). Potential explanations for this increased risk include inadequate surgery for the primary tumor (20,22), a greater prevalence of certain histopathologic features, such as an extensive intraductal component or a major mono-

nuclear cell reaction (5,11,13), or tumors of high histologic grade (5). However, young women with EIC-negative tumors (13), and adequate excision as demonstrated by negative margins of resection (19) or the use of quadrantectomy (7), or the absence of certain pathologic features (12) continue to have an increased risk of breast recurrence. Young women undergoing mastectomy also have an increased risk of local regional recurrence (21,26), which appears to be similar to that following breast-conservation therapy. Therefore, the increased risk of local regional recurrence in young women appears to be independent of the surgical procedure for the primary tumor. The benefit of adjuvant chemotherapy in young women with breast cancer requires further investigation. Data from the Early Breast Cancer Trialists Collaborative Group (23) demonstrated a greater reduction in the annual odds of recurrence or death in women under the age of 50 with multiagent chemotherapy when compared with women > 50 . However, there is increasing evidence that the young premenopausal woman may respond less well to adjuvant systemic therapy when compared with the older, premenopausal woman. During the conference, data from the Southwest Oncology Group (SWOG) as well as the NSABP B13 trial for node-negative, estrogen-receptor negative women were presented that suggest less of a benefit from adjuvant chemotherapy in the young woman. Also, there is emerging evidence that young women with metastatic breast cancer may respond less well to systemic chemotherapy (24,25). Women under the age of 40 with responding metastatic disease undergoing dose-intense chemotherapy and autologous bone marrow transplant were reported by Karen Antman to have a decreased disease-free survival when compared with older women.

The role of hormonal management in premenopausal women with breast cancer has been evaluated in a number of prospective randomized trials. The Early Breast Cancer Trialists Collaborative Group (23) reported a greater benefit in terms of decreased recurrence and mortality for postmenopausal women when compared with premenopausal women. However, the effect of tamoxifen on the very young woman with breast cancer is unknown. Medical ovarian ablation in contrast to surgical ovarian ablation is reversible and is currently under investigation.

The young woman with breast cancer has the potential for long-term survival and therefore the development of late treatment-related sequelae. A complication of treatment with either chemotherapy or radiation therapy is the development of second malignancies, i.e., acute nonlymphocytic leukemia, second non-

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breast malignancies, and contralateral breast cancer. To date, the risk of a second malignancy from treatment appears not to exceed its benefit.

In summary, the weight of the evidence presented suggests that young women with breast cancer have an increased risk for all patterns of failure and a decreased survival with current treatment regimens when compared with older women. For future studies, the definition of young age should be standardized and since there are limited numbers of young women with breast cancer, every effort should be made to design prospective randomized trials that will answer important questions in these women. In the interim, further analysis of the completed randomized trials should be performed with special emphasis on young age. The National Cancer Institute Conference on Breast Cancer in Young Women has served as a major initiative for all investigators to concentrate on this most important issue and it has identified key areas where our knowledge is either lacking or minimal.

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Survival Patterns Among Younger Women With Breast Cancer: the Effects of Age, Race, Stage, and Treatment

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Several hundred studies of breast cancer survival are published each year; yet few of them include women under the age of 50, and almost none of them specifically examine prognosis among women in their 20s through 40s. The few published reports that analyze survival after breast cancer among these young patients do not provide a consistent or definitive description of their survival experience. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program offers a unique opportunity to analyze breast cancer survival in depth among younger women. In this report, survival patterns of all black and white women diagnosed with breast cancer between 1983 and 1989, aged 20 and older, microscopically confirmed, and undergoing surgery, in the SEER program have been analyzed. There are 77 368 women included in this study, 92.8% of whom were white. Less than 1% (562 patients) of these breast cancer patients were between the ages of 20 and 29, 6.5% (5062 patients) were 30-39, and 15.2% (11 789 patients) were 40-49. Survival was calculated utilizing a mixture model to evaluate the cause-specific hazards of dying of breast cancer versus dying of other causes of death. We investigated the hazard of dying of breast cancer versus other causes of death by age at diagnosis, year of diagnosis, extent of disease and diagnosis, and treatment. Stage was stratified into three categories: 1) cases with no axillary lymph node involvement, 2) cases with axillary lymph node involvement, and 3) cases with distant metastases. Prognosis for black and white breast cancer patients was evaluated separately. The youngest women have the highest probability of dying of breast cancer. The cumulative probability of death due to breast cancer within 5 years after diagnosis among women in the age group 20-29 was 26.4% for white women and 33.7% for black women. At age 30-39, this probability was 20.1% for white women and 32.4% for black women. As one might expect, older women have a greater probability of dying of other causes. The key question in this study is at what age does breast cancer have the greatest survival impact upon women. Our results clearly demonstrate that breast cancer takes its greatest toll on the youngest women. In terms of future research, it is imperative that clinical trials encompass women diagnosed with breast cancer at all ages, not just those at age 50 and older. It is also important to evaluate survival patterns among women in their 20s, 30s, and 40s and to contrast their prognosis with that of older

women. The poor survival experience of these young women also must be measured in terms of person-years of life lost, the impact on families, and loss of productive years to society. Finally, clinical trials should be designed to determine whether women in these younger age groups have different responses to treatment than older women. Characteristics such as hormonal status, metabolism, and co-morbid conditions that vary across the lifespan may well influence treatment. [Monogr Natl Cancer Inst 16:69-77, 1994]

The effects of age on survival after breast cancer have not been well defined. An early study of causes of death among long-term survivors of breast cancer observed that women under 35 years of age and women 35-44 had the largest proportion of excess deaths due to breast cancer at both 5-10 and 10-15 years after diagnosis when compared with all other age groups. Evaluating causes of death among 4100 women in Connecticut who had survived breast cancer for 25 years, Ederer et al. (1) found that breast cancer as a cause of excess death at both 5-10 and 10-15 years after diagnosis occurred most often among women younger than 35 at diagnosis and declined continuously across each of seven older 10-year age groups. An early clinical series of 3558 women also reported that the largest proportion of breast cancer patients dying of breast cancer was in the youngest age group, 21-50 years of age. They found that 96.5% of the women in this age group died of breast cancer, in contrast to 89.8% in the age group 51-70 and 77.5% in the age group 71-100 (2). More recent population-based studies of breast cancer survival continue to observe lower survival among women under 35 (3-5). Utilizing data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for breast cancer cases diagnosed between 1973 and 1979, Ries et al. (3) reported relative survival among white women that ranged from 67% for women under 35 to 75% for women 45-54 years of age; for black women survival ranged from 54% among women younger than 35 to 68% among women 75 and older. These studies did not explain whether the

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excess breast cancer mortality was due simply to the lack of competing causes of death among younger women or whether there are characteristics of breast cancer in this younger group that produce a more lethal form of the disease.

The most recent report from the SEER Program provides age-specific relative survival among women diagnosed with breast cancer between 1983 and 1988. The lowest rate of survival after breast cancer among white women was observed among women younger than 45 at diagnosis. Among black women, the lowest rate of survival was observed both for women younger than 45 and 75 and older at diagnosis (4).

Over the past 12 years, several studies have assessed the influence of age on breast cancer survival among women of different ethnic groups (3,5-11). These studies have observed diverse survival patterns across various ethnic groups. They describe 1) poorer survival or excess mortality due to breast cancer among the youngest women, particularly women in their 20s and 30s at diagnosis, for whites and blacks (3,5,6); 2) better survival among Japanese women at all ages (7,10); 3) interactions between age and stage at diagnosis (8,9); and 4) no difference in survival among pre- and post-menopausal women in a population where women are, on the average, 20 years younger at diagnosis for breast cancer than is observed in western cultures (11).

Social class has been investigated as an explanatory factor for the survival differences observed across various age groups (12-15). In one of these studies (12) it was observed that, although the youngest women (25-44 years) experienced the lowest survival overall, when social class was evaluated, in the highest social class, younger women had poorer survival, but in the lowest social class, women 25-44 had the highest survival. Another study (15) found just the opposite, that the lowest survival was seen among women under age 50 at diagnosis and in the lowest socioeconomic status category. Bassett and Krieger (13) reported that, when comparing black and white women with breast cancer, survival differences were drastically reduced when these rates were adjusted for age, stage at diagnosis, and social class. Dayal et al. (14) found that the lowest survival at 1-5 years after diagnosis among the lowest socioeconomic status groups was experienced by women younger than 40 years at diagnosis and that the greatest discrepancy between these women (38% survival), women 40-59 years (75% survival) and 60 years and older (60% survival) was at 2-3 years after diagnosis.

Very few of the most recent studies of breast cancer survival include age in their analysis. Among more than 400 papers concerned with breast cancer survival and published during 1990-1992, there were fewer than 20 that evaluated survival among women younger than 50. In most studies, age is not included in the analyses. When age is included, it most often is evaluated separately, rather than in conjunction with other variables. For example, studies by Bergman et al. (16,17) evaluate breast cancer survival experience among "younger" versus "older" women, defining younger as 55-64! A study of the influence of hormone receptor status on survival after breast cancer includes only women 50 and older (18), even though it is known that there are considerable differences in hormone receptor status among women younger than 50 compared with those 50 and

older (19). Other studies (20,21) evaluate well-known prognostic factors such as tumor size and axillary lymph node involvement and do not even consider the effects of age. One very interesting study investigated the effects on survival of known risk factors for breast cancer, including age, but did not evaluate the influence of age on any of these etiologic factors (22).

It is clear from the studies published to date that the role of age in the prognosis of breast cancer is poorly defined. To launch a discussion of and to develop hypotheses regarding the effects of age on breast cancer survival among women in the United States, we have conducted a population-based investigation of breast cancer survival in terms of age at diagnosis, race, stage of disease at diagnosis, and treatment. Data from the National Cancer Institute's SEER Program provides a unique resource for an evaluation of the force of mortality due to breast cancer among American women.

Materials and Methods

Case Definition Criteria

The SEER Program, sponsored by the National Cancer Institute, is the source of nationally representative data for the United States describing our population's experience with cancer. From these data, detailed analyses are performed to understand patterns of cancer incidence, mortality, and survival. Initiated in 1973, the SEER Program provides population-based cancer information for five states (Connecticut, Iowa, Hawaii, New Mexico, and Utah) and four metropolitan areas (Atlanta, Detroit, San Francisco-Oakland, and Seattle). Participants are required to perform active follow-up on all living cases each year; therefore, complete follow-up is available for over 90% of the cases. Follow-up methods include linkage with death certificate information; physician, hospital, and hospice inquiry; patient or family interview; linkage with voter registration and driver registration information; and linkage with national Health Care Financing Administration information.

This study encompasses breast cancer cases from all nine geographic regions. Cases selected were diagnosed from 1983 through 1989. These years were selected to coincide with the adoption of breast conservation therapy and with more extensive utilization of mammography for breast cancer screening. Demographically, cases were selected to include black and white women diagnosed with breast cancer at age 20 or older. In addition, cases were invasive, microscopically confirmed, and had at least surgical treatment of breast cancer.

The four major variables utilized in this analysis are: age, race, extent of disease at diagnosis, and treatment. Age is categorized into seven groupings: 20-29 years, 30-39, 40-49, 50-59, 60-69, 70-79, and 80 or older. Race includes two groups: black and white. Extent of disease at diagnosis is grouped into three categories: localized (confined to the breast tissue and fat, including nipple and/or areola), regional (extension into the axillary lymph nodes), and distant (any extension beyond the breast and axillary lymph nodes). Treatment was categorized into four groups: lumpectomy plus radiation therapy, lumpectomy without radiation therapy, mastectomy with radiation therapy, and mastectomy without radiation therapy. In the stratified analyses, probabilities are adjusted for the variables not utilized

for stratification. For example, analyses evaluating death due to breast cancer or death due to other causes by age are adjusted for stage at diagnosis and treatment. When treatment is the variable utilized to stratify the data, the analysis includes adjustment for age and stage at diagnosis.

Statistical Methods

A major purpose of this study was to assess the contribution of breast cancer to mortality. Therefore, subjects could experience several distinct events while under observation (death due to breast cancer and death due to other causes). These events are classified as competing risks, since the occurrence of one event precludes the occurrence of the other. Thus, death caused by breast cancer and death due to any other cause (including unknown cause of death) are the two competing risk events. However, these competing risks are dependent in that those at highest risk of death due to breast cancer are thought to be at lowest risk of other causes of death. As a result, it is not appropriate to treat those with experience of other causes of death as censored observations (23).

Pooling of repeated observations (PRO) is the method utilized in this analysis. Treating each 6-month interval as a mini follow-up study, the PRO method pools observations over all intervals to examine the hazard functions of breast cancer deaths and deaths due to other causes. Thompson (24) showed that this model (PRO) leads back to the proportional hazards model as the length of the intervals approaches zero, while Abbott (25) applied these models to grouped survival data and obtained results similar to those obtained from the proportional hazards model in the grouped event time setting. Additionally, D'Agostino et al. (26) showed that pooled logistic regression approximates the time-dependent covariate Cox regression model by allowing covariates to change at each time interval, if the response variable is dichotomous. Unlike the Cox proportional hazards model, this model can also deal with multinomial response, and no assumption is made among each category of response, except that the summation of all the probabilities equal one.

The relation of the pooled observations to the breast cancer survival is analyzed using polytomous logistic regression. Polytomous logistic regression, in turn, is utilized to predict the probability of breast cancer death (p_1), the probability of death due to other causes (p_2), and the probability of remaining alive (p_3). When the intervals between measurements are short, the probability of an event within an interval is small and the intercept for the pooled logistic is constant across intervals, the PRO method and Cox proportional hazard model are asymptotically equivalent (27). In the three-category model utilized, we have two logit functions: one for p_1 versus p_3 and another for p_2 versus p_3 . The logit for comparing p_2 to p_1 may be obtained as the difference between the logit of p_2 versus p_3 and the logit of p_1 versus p_3 (28).

$$p_1 = \exp(g_1(x)) / [1 + \exp(g_1(x)) + \exp(g_2(x))]$$

$$p_2 = \exp(g_2(x)) / [1 + \exp(g_1(x)) + \exp(g_2(x))]$$

$$p_3 = 1 - p_1 - p_2,$$

where $g_1(x) = \ln[p_1/p_3] = \alpha_1 + \beta_1 X$, and $g_2(x) = \ln[p_2/p_3] = \alpha_2 + \beta_2 X$. X is covariate matrix. β_1 and β_2 are coefficient matrixes for $g_1(x)$ and $g_2(x)$, respectively.

The strengths of this approach to evaluating survival after breast cancer among younger women are as follows: 1) This approach can accommodate dichotomous, ordinal, or nominal outcome easily. 2) This approach has less assumptions than the Cox proportional hazard model. But under some conditions, they both tend to yield similar results. 3) This approach can easily be transformed to parametric models (such as Weibull, exponential, Gompertz, etc.).

The limitations of utilizing this approach to evaluating survival after breast cancer include: 1) The model assumes that the logit of the probability of event in an interval, conditional that the event has not occurred prior to the interval, is a linear function of covariates and a constant term specific to the interval. If the interval is too large, it may not be appropriate to assume baseline hazard function is a constant for an interval. 2) Summary statistics may not be meaningful because each subject may contribute more than one line of data to the analysis and the model assumes each line corresponds to an independent subject.

In this model, alive ($Y = 3$) is the reference outcome. The odds ratio of outcome $Y = j$ (1:breast cancer death, 2:death due to other causes) versus outcome 3 for covariate values of $x = a$ versus $x = b$ is ψ ; $(a,b) = [P(Y = j/x = a) * P(Y = 3/x = b)] / [P(Y = j/x = b) * P(Y = 3/x = a)]$ $j = 1,2$.

Patients in this study were diagnosed during 7 different years, thus contributing variable lengths of follow-up to the analysis. To reduce the potential for confounding by differential follow-up time, we controlled for year of diagnosis when assessing the effects of other variables.

Confidence intervals are obtained in exactly the same manner as in the binary outcome model.

Results

Subject Characteristics

There were 77 368 women diagnosed with breast cancer who met the study definition criteria. Of these, 92.8% were white and 7.2% were black (Table 1). Among white women, 6.7% were younger than 40 at diagnosis, as were 14.1% of black women (Table 1). Among white women diagnosed with localized disease, 5.9% were under age 40, as were 9.1% of those with regional disease and 5.4% of those with distant disease (Table 1). Among black women diagnosed with localized disease, 13.9% were younger than 40, as were 15.9% of those diagnosed with regional disease and 11.9% of those diagnosed with distant disease (Table 1).

With regard to treatment, among white women who had breast-conserving treatment, 9.6% were younger than 40 at diagnosis, as were 19.9% of black women. Of those who had mastectomy without radiation therapy, 5.9% of white women and 12.3% of black women were younger than 40 at diagnosis (Table 1).

Breast Cancer Deaths

In Table 2, we present, for black and white women, the cumulative probability of death due to breast cancer within 5 years after diagnosis by stage, treatment, and age at diagnosis. These data clearly demonstrate that, in every situation analyzed,

Table 1. Female breast cancer, SEER program, 1983-1989: distribution by race, stage at diagnosis, initial course of treatment, and age at diagnosis

	Age at diagnosis, y							Total
	20-29	30-39	40-49	50-59	60-69	70-79	≥80	
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patient (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
<i>White females</i>								
Stage at diagnosis								
Localized (no axillary lymph node involvement)	226 (0.54)	2234 (5.36)	5837 (14.00)	7655 (18.36)	11 552 (27.70)	9777 (23.45)	~4419 (10.60)	41 700 (58.08)
Regional (with axillary lymph node involvement)	183 (0.89)	1671 (8.16)	3750 (18.32)	4453 (21.75)	5267 (25.73)	3733 (18.24)	1413 (6.90)	20 470 (28.51)
Distant metastases	51 (0.53)	472 (4.90)	1072 (11.13)	1666 (17.30)	2479 (25.74)	2277 (23.64)	1613 (16.75)	9630 (13.41)
Treatment								
Lumpectomy with radiation	93 (0.81)	1008 (8.83)	2322 (20.33)	2551 (22.34)	3174 (27.79)	1804 (15.80)	469 (4.11)	11 421 (15.91)
Lumpectomy without radiation	31 (0.64)	241 (4.98)	558 (11.54)	718 (14.85)	988 (20.43)	1058 (21.88)	1242 (25.68)	4836 (6.73)
Mastectomy with radiation	58 (1.13)	427 (8.34)	894 (17.47)	1098 (21.45)	1398 (27.32)	958 (18.72)	285 (5.57)	5118 (7.13)
Mastectomy without radiation	278 (0.55)	2701 (5.36)	6885 (13.65)	9407 (18.66)	13 738 (27.24)	11 967 (23.73)	5449 (10.81)	50 425 (70.23)
Total	460 (0.6)	4377 (6.1)	10 659 (14.8)	13 774 (19.2)	19 298 (26.9)	15 787 (21.9)	7445 (10.4)	71 800 (100.0)
<i>Black females</i>								
Stage at diagnosis								
Localized (no axillary lymph node involvement)	44 (1.64)	328 (12.22)	538 (20.04)	545 (20.30)	618 (23.02)	472 (17.58)	140 (5.21)	2685 (48.22)
Regional (with axillary lymph node involvement)	39 (2.16)	248 (13.75)	400 (22.17)	413 (22.89)	417 (23.12)	223 (12.36)	64 (3.55)	1804 (32.39)
Distant metastases	19 (1.76)	109 (10.10)	192 (17.79)	227 (21.04)	250 (23.17)	186 (17.24)	96 (8.90)	1079 (19.38)
Treatment								
Lumpectomy with radiation	24 (2.96)	138 (17.02)	208 (25.65)	180 (22.19)	149 (18.37)	96 (11.84)	16 (1.97)	811 (14.56)
Lumpectomy without radiation	11 (2.63)	58 (13.84)	56 (13.37)	62 (14.80)	107 (25.54)	58 (13.84)	67 (15.99)	419 (7.52)
Mastectomy with radiation	8 (1.37)	85 (14.58)	121 (20.75)	149 (25.56)	127 (21.78)	72 (12.35)	21 (3.60)	583 (10.47)
Mastectomy without radiation	59 (1.57)	404 (10.76)	745 (19.84)	794 (21.15)	902 (24.02)	655 (17.44)	196 (5.22)	3755 (67.44)
Total	102 (1.8)	685 (12.3)	1130 (20.3)	1185 (21.3)	1285 (23.1)	881 (15.8)	300 (5.4)	5568 (100.0)

black women have a higher probability of dying of breast cancer than white women. For localized breast cancer and for lumpectomy with radiation, black women have a death rate due to breast cancer that is nearly twice as high as that experienced by white women. Age clearly is a critical variable in prognosis, with black and white women 20-29 and 30-39 years of age at diagnosis having the highest proportion of deaths due to breast

cancer, followed by women 50-59 for blacks and 60-69 for whites.

Both black and white women 20-29 and 30-39 years of age have a higher probability of dying of breast cancer than women in any other age group across the entire follow-up period (Fig. 1). In each 6-month interval, white women aged 20-29 at diagnosis of breast cancer die of breast cancer at a rate that is 45%-50% higher than women with the lowest rate of death due to breast cancer; this excess breast cancer mortality among women 30-39 is 25%-37% greater than women with the lowest breast cancer death rate. Among black women who are 20-29 at diagnosis of breast cancer, breast cancer deaths occur 37%-42% more often than among women with the lowest breast cancer mortality, while among black women 30-39 at diagnosis, the excess ranges from 34% to 40%.

In Table 3, odds ratios and their 95% confidence intervals are presented to assess the effect of each study variable on deaths due to breast cancer. These data demonstrate that race, age at diagnosis, stage at diagnosis, first course of treatment, and year of diagnosis each have a significant influence on dying of breast cancer. Black women are more likely to die of breast cancer than white women. Women 20-29 years old at diagnosis are more likely to die of breast cancer than women in any other age group and women 30-39 years old at diagnosis are the second most likely age group to die of breast cancer. Increasingly advanced stage of disease at diagnosis shows large increases in the probability of dying of breast cancer. Women treated by lumpectomy and radiation therapy as their first course of treatment

Table 2. Cumulative probability of breast cancer death 5 years after diagnosis

	% dying	
	White females	Black females
Stage of disease at diagnosis		
Localized	5.7	10.4
Regional	16.7	26.4
Distant	38.7	50.8
Treatment		
Lumpectomy with radiation	14.1	27.9
Lumpectomy without radiation	18.0	29.6
Mastectomy with radiation	20.4	35.5
Mastectomy without radiation	13.7	23.1
Age at diagnosis, y		
20-29	26.4	33.7
30-39	20.1	32.4
40-49	15.1	27.8
50-59	14.1	29.3
60-69	16.7	22.5
70-79	13.2	21.1
≥80	15.1	17.8

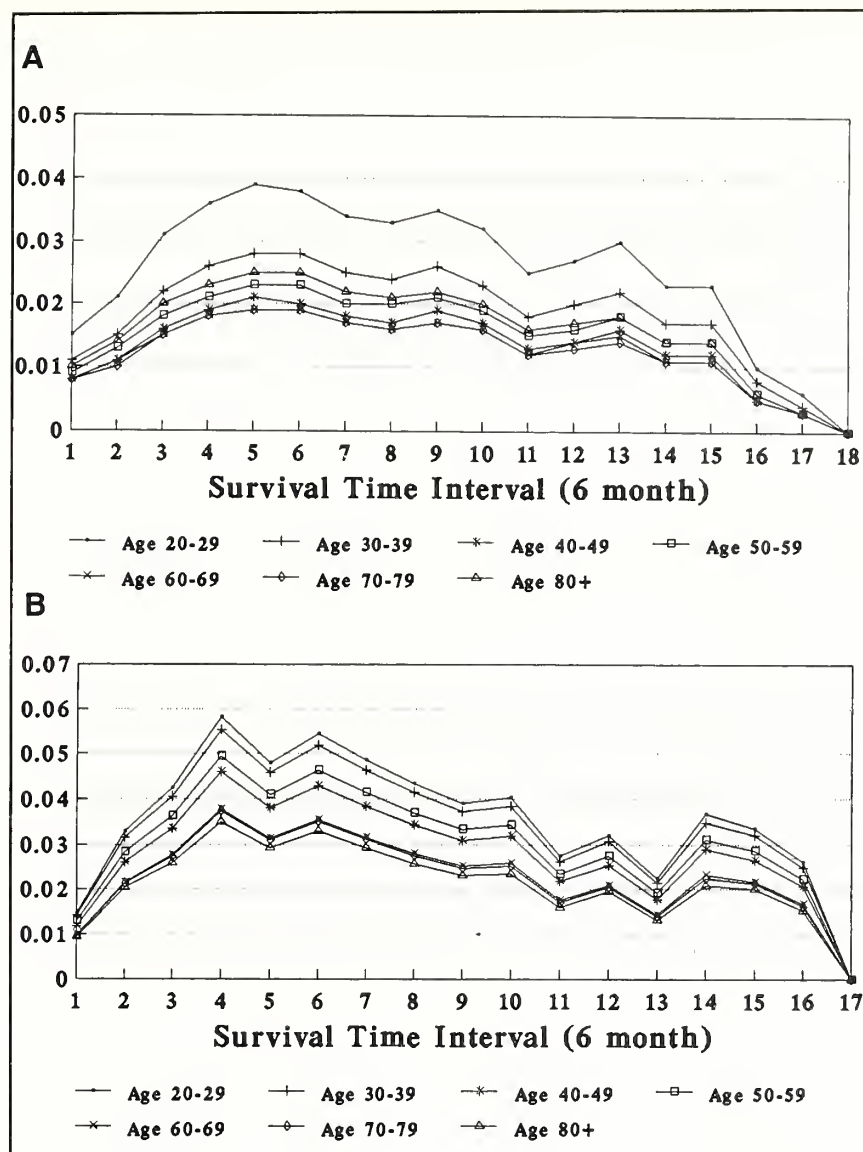


Fig. 1. Probability of death due to breast cancer. A) White females. B) Black females.

have the lowest risk of dying of breast cancer when compared with women in three other treatment groups. Finally, year of diagnosis effects the probability of dying of breast cancer. Each year from 1983 through 1989 demonstrates a significant reduction in the odds of death due to breast cancer.

Deaths Among Breast Cancer Patients From Other Causes

Similar analyses of deaths due to causes other than breast cancer do not demonstrate a greater impact among younger women. In Table 4, we observe a mixed effect of age on the probability of dying of other causes after a diagnosis of breast cancer. At each stage of disease and for both black and white women, the oldest women (≥ 80 years of age) are significantly more likely to die from some cause other than breast cancer than are women 20-29.

In Fig. 2, the pattern of deaths due to causes other than breast cancer by age category is the inverse of that seen for deaths due to breast cancer. Both black women and white women in the oldest age groups are most likely to die from other causes after a diagnosis of breast cancer. Women who are 80 and older or in

their 70s at diagnosis have a particularly higher probability of dying from other causes than women in any other age group.

Summary and Conclusions

When survival after a diagnosis of breast cancer is evaluated in this population-based national sample of breast cancer cases; when race, stage of disease at diagnosis, and treatment are held constant; and when the effects of deaths due to breast cancer are the focus of the analysis, we observe clearly that the force of breast cancer mortality is greatest among the youngest women. Women in these younger age groups—20-29 and 30-39—constitute about 7% of white breast cancer patients and 14% of black breast cancer patients. They account for 9.7% and 17.2% of deaths due to breast cancer among white and black women, respectively. Relative survival of these patients by age and by race also was calculated utilizing the Cox proportional hazards model. This was done to determine whether the age patterns observed utilizing the PRO method would be consistent with the results of a relative survival analysis. Relative survival analysis also showed higher rates of death among younger breast cancer

Table 3. Probability of death due to breast cancer: effects of race, age at diagnosis, stage at diagnosis, first course of treatment, and year of diagnosis

	No. of patients	Odds ratio	95% confidence interval	
Race				
White women	71 800	1.00	—	—
Black women	5568	1.58	1.48	1.68
Age at diagnosis, y				
20-29	562	1.00	—	—
30-39	5062	0.77	0.64	0.93
40-49	11 789	0.56	0.47	0.68
50-59	14 959	0.62	0.51	0.74
60-69	20 583	0.52	0.43	0.62
70-79	16 668	0.51	0.43	0.62
≥80	7745	0.68	0.56	0.81
Stage at diagnosis				
Localized (no axillary lymph node involvement)	44 385	1.00	—	—
Regional (with axillary lymph node involvement)	22 274	3.33	3.15	3.51
Distant metastases	10 709	8.01	7.58	8.46
First course of treatment				
Lumpectomy with radiation	12 232	1.00	—	—
Lumpectomy without radiation	5255	1.67	1.52	1.84
Mastectomy with radiation	5701	1.63	1.50	1.77
Mastectomy without radiation	54 180	1.10	1.03	1.18
Year of diagnosis				
1983		1.00	—	—
1984		0.88	0.83	0.95
1985		0.87	0.81	0.93
1986		0.84	0.79	0.90
1987		0.78	0.72	0.84
1988		0.65	0.61	0.69
1989		0.64	0.57	0.73

Table 4. Probability of death due to causes other than breast cancer: effects of age at diagnosis*

Age at diagnosis, y	Localized OR	Regional OR	Distant OR
White females			
20-29	1.00	1.00	1.00
30-39	0.56	0.80	0.32
40-49	0.41†	0.53	0.43
50-59	0.78	0.80	0.58
60-69	1.55	1.50	0.92
70-79	3.31†	2.67†	1.28
≥80	7.43†	5.53†	2.82†
Black females			
20-29	1.00	1.00	1.00
30-39	0.42	1.16	2.93
40-49	0.44	1.31	1.97
50-59	0.75	1.23	3.09
60-69	1.19	2.37	4.96
70-79	1.96	3.73	6.31
≥80	4.58†	5.62†	7.75†

*OR = odds ratio.

†Significant at $P < .05$.

patients, similar to the patterns we reported based on the PRO method.

What are the explanations for this survival pattern? Why are the youngest women, presumably the most healthy, the most likely to succumb to their breast cancer? Even when these young women are diagnosed with early-stage breast cancer, they are more likely to die as a result of this disease than women in any of the older age groups. There are various possible explanations for the poor survival experience of younger women with breast cancer: 1) perhaps their higher estrogen levels induce a more rapid tumor growth rate; 2) perhaps other prognostic factors that reduce survival are more common among younger women; 3) perhaps their higher mortality from breast cancer is due, in part, to the lack of competing causes of death; and 4) perhaps the biology of breast cancer differs significantly among the youngest women in contrast with women in their 50s and older. Each of these hypotheses requires thorough investigation.

Some direction for future research is provided by earlier studies that have considered the influence of obesity, nutritional status, social class, delay in seeking medical consultation, hormone receptor status, oral contraceptive use, and ethnic background. Two areas that may be the most promising in our efforts to understand the excess mortality resulting from breast cancer in younger women are hormonal factors and obesity.

Studies by Mason et al. (29,30) investigated estrogen receptor and progesterone receptor and found that women younger than 50 at diagnosis who were both estrogen-receptor negative and progesterone-receptor negative had significantly shorter survival when their breast cancer was discovered in the winter or fall than when it was detected in the spring or summer. They hypothesize that hormonal factors may vary by season of the year and thus influence the hormone-dependent growth of breast tumors. In a study of the influence of oral contraceptive use on breast cancer survivorship, investigators found that women who began oral contraceptive use before age 20 had 5-year breast cancer survivorship of 62%, compared with 78% for those who began oral contraceptive use at ages 20-25 and 86% for those who began after age 25 (31). Both studies provide evidence that hormonal attributes of younger women have a negative effect on survival. It has been suggested recently that timing of excision of breast tumors during the woman's menstrual cycle influences prognosis (32,33). One study (30) demonstrated that women who had had surgery during days 3-12 after their last menstrual cycle had poorer disease-free and overall survival than women having surgery at any other time after their last menstrual cycle. The other study (34) found that women having surgery during the follicular phase had a 50% higher risk of recurrence than other women and a shorter disease-free survival. These studies offer one possible explanation for the greater mortality from breast cancer observed among younger women. It will be important to determine whether this pattern is similar among all premenopausal breast cancer patients, or whether it differs among women in their 20s, 30s, and 40s at breast cancer diagnosis. Further investigation is essential to specify hormonal factors associated with death due to breast cancer and to clarify their relationship to other prognostic factors.

Several investigators have shown that obesity is correlated with poorer survival after breast cancer (34-36). Some studies

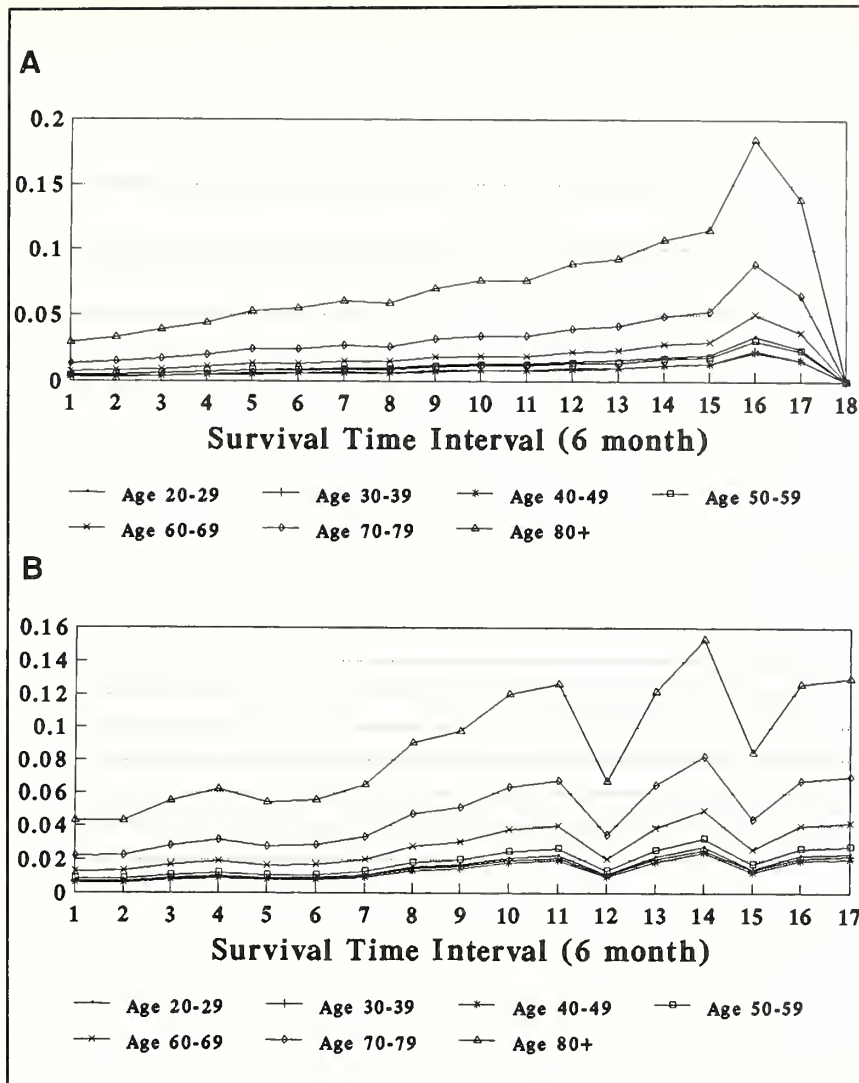


Fig. 2. Probability of death due to causes other than breast cancer. A) White females. B) Black females.

have evaluated the influence of age on the effects of obesity (35-36) and others have not (34-37). It has been demonstrated that women who are obese at diagnosis of breast cancer and during the year before diagnosis have shorter survival than women who are not obese (33). Coates et al. (37) have shown that black women with breast cancer are more likely to be obese than white women, which may explain some of the survival differences between these two races. In two studies that did investigate the relationship between age and obesity and survival after breast cancer, one (35) found that women at any age who are obese have about a 15% lower survival rate than women who are not obese. They also found that women 55 and older at diagnosis of breast cancer are twice as likely to be obese as women 40-54 at diagnosis. Women younger than 40 were not included in this study. Another study found that women diagnosed with breast cancer at age 30-49 and with the highest Quetelet Index scores had poorer survival than older women, but only when their breast cancers were diagnosed at stages I and II (36). These studies provide some suggestive leads for further investigation. In addition, the interaction among age, obesity, and hormonal status and their effects on survival should be carefully evaluated across the lifespan.

Studies of socioeconomic status and breast cancer demonstrate that women in lower social classes have poorer breast cancer survival, yet the age patterns reported are not consistent (12,13,15). The influence of social class seems to explain some of the differences in survival seen between blacks and whites (13), but socioeconomic characteristics have not been considered in the context of other prognostic factors such as obesity, hormonal status, stage of disease at diagnosis, and adherence to treatment protocols. Similarly, age differences in survival after breast cancer have been observed across diverse ethnic groups (3,5-7), but have not been explained in terms of their relationship to other prognostic factors. One study (10) does suggest that younger Japanese women may have better survival after breast cancer than younger Caucasian women because of their lower mean body weight and lower fat intake.

A recent study (38) reports that the shortest time between symptom recognition and medical consultation occurs among women 20-49 and that there is no difference in response to symptoms at this age between blacks' and whites' behaviors prior to a breast cancer diagnosis. This raises a question as to whether early medical intervention can improve outcome in this youngest age group.

Studies of long-term survival suggest that the pattern of poorer survival among younger women may change over time (39,40). In a study (39) of 30-year survival after breast cancer, investigators found that women 20-34 at diagnosis had the worst survival during the first 5 years after diagnosis, reached "normal" survival at about 10 years, and by 15-30 years had the best survival. A study in Sweden had similar results, with women younger than 30 at diagnosis having the lowest survival at 5 years after diagnosis, but by 10 and 15 years after diagnosis they had higher survival than most age groups (40). Questions of how various prognostic factors influence the course of disease over long time periods are critical for the youngest women being diagnosed with breast cancer.

Even among women diagnosed with metastatic breast cancer, age influences survival. One study (41) observed that age was the third most important prognostic factor after performance status and metastatic site. The longest median survival (39.8 months) was observed among women 85 and older at diagnosis, while women 55-64 at diagnosis had a median survival of 16.2 months and women in the youngest group included in the study (aged 45-54) had an intermediate length of survival—21.2 months.

Early detection of breast cancer among this youngest group of women poses a particular dilemma. They are not good candidates for routine mammography. Therefore, it is particularly important that we understand those factors most likely to predict poor survival after breast cancer, particularly characteristics that can be modified, such as obesity and perhaps hormonal status.

Our results clearly demonstrate that, among women in the United States, breast cancer is more lethal among women diagnosed with this disease in their 20s and 30s than it is among any other age groups. A well-defined research agenda is essential if we are to disassemble this puzzle and prevent unnecessary deaths resulting from breast cancer. It also is essential to evaluate the impact of early death after breast cancer among these young women in terms of the impact on their families, the loss of productive years to society, and other critical social costs.

Recommendations

A three-part research agenda is appropriate to answer the many questions raised by the excess mortality due to breast cancer seen among women in their 20s and 30s at diagnosis.

First, etiologic studies are essential to specify the factors associated with poor breast cancer survival. These studies must encompass women of all age categories and of diverse ethnic groups. Rather than evaluating one or two potential prognostic factors, these studies must assess the complex of events that results in early death from breast cancer: age, ethnicity, obesity, hormonal status, socioeconomic status, stage of disease at diagnosis, and adherence to medical care. Particular attention should be given to factors that may vary across the life span and modify the force of mortality from breast cancer, such as comorbid conditions, hormonal status, metabolism, and obesity. Such studies must be designed to oversample younger women, since breast cancer occurs at much lower rates among these women than among older women.

Second, clinical trials must incorporate younger women in order to compare their responses to treatment in contrast to the responses of older women. It is essential to make specific efforts to recruit younger women into clinical trials and to ensure that diverse ethnic groups are represented. Many of the factors that vary over the lifespan and may be associated with prognosis may act by effecting different responses to treatment among women of different ages. Prevention trials also must attend to the inclusion of these young women whenever it is appropriate within the context of the study protocol.

Third, psychosocial and economic studies are needed to measure the impact of excessive breast cancer deaths among the families of these women in their 20s and 30s. The losses to society in terms of productive years also should be measured among these young women and contrasted to similar losses among older women.

The ultimate objective of these studies should be to determine factors that can modify the survival and mortality experience of younger women with breast cancer. It may be that survival can be extended among some of these young women with breast cancer and that some of the deaths due to breast cancer can be prevented.

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Breast Cancer in Young Women: Issues in Local Therapy

Monica Morrow, Cathy Hassett*

Although age has been studied as a prognostic factor in breast cancer, little attention has been paid to its role in the selection and outcome of local therapy. A review of 42 breast cancer patients less than 40 years of age treated at the University of Chicago from 1989 to 1992 demonstrated that of women with stage 0, I, or II disease, 37% had medical contraindications to breast preservation compared with 25% of women over 40. Twenty-one percent of young women eligible for conservation opted for mastectomy and reconstruction compared with 9% of their older counterparts. Only 4% of women in either age group selected mastectomy alone as therapy. The literature on the relationship of age to local failure after breast conservation and the long-term morbidity of the local therapy of breast cancer is reviewed. Further research to clarify issues in local therapy in young patients is proposed. [Monogr Natl Cancer Inst 16:79-84, 1994]

Breast cancer in young women has been a subject of interest for many years. The majority of reports on this subject have analyzed the clinical presentation and prognosis in younger women (1-4). To provide sufficient numbers for analysis, women treated over long-time intervals were usually studied. The vast majority of these women underwent mastectomy and received no systemic adjuvant therapy. In the 1980s, dramatic changes occurred in the approach to the local therapy for breast cancer. Prospective, randomized trials (5,6) demonstrated that survival after lumpectomy, axillary dissection, and radiotherapy was equivalent to survival after mastectomy. Additional studies (7-12), attempting to define selection criteria for breast-conserving surgery, suggested that breast recurrences might be more common in young women treated with a breast-sparing approach.

Little is known about the impact of patient age on local therapy or the long-term sequelae of local therapy. Important unanswered questions exist regarding the influence of patient age on selection of surgical procedure, local failure rates after breast-conserving surgery or mastectomy, and the long-term morbidity of these procedures. This article will review the available data on the selection and outcome of local therapy in young breast cancer patients.

Selection of Local Therapy

To determine the impact of age on selection of a local therapy for breast cancer, we reviewed our experience at the University

of Chicago Multidisciplinary Breast Cancer Program from July 1989 through December 1992. During this interval, 42 women less than 40 years of age underwent primary breast cancer therapy. Women between the ages of 41 and 50 ($n = 67$) treated in 1990 and 1991 were used for comparison. All patients were reviewed at presentation by a multidisciplinary team consisting of surgeons, medical oncologists, radiation oncologists, reconstructive surgeons, a pathologist, a mammographer, and nursing and social service personnel to discuss eligibility for breast conservation or immediate reconstruction. Contraindications to breast conservation included multiple primary tumors, diffuse indeterminate microcalcifications on mammogram, and the ability to achieve negative margins after two surgical excisions. Large tumors in small breasts, in which a cosmetically satisfactory excision could not be carried out, were also considered a contraindication. These contraindications conform to the following standards agreed upon by the American College of Radiology, American College of Surgeons, College of American Pathologists, and the Society of Surgical Oncology (13):

Absolute contraindications:

- First and second trimester pregnancies
- Two or more gross tumors in separate quadrants
- Diffuse malignant or indeterminate microcalcifications
- History of prior therapeutic irradiation to the breast region

Relative contraindications:

- History of collagen vascular disease
- Large tumor-to-breast ratio resulting in major cosmetic alteration
- Tumor location requiring nipple loss (a contraindication only if unacceptable to the patient)

The presence of significant comorbid conditions making a prolongation of general anesthesia inadvisable was considered a contraindication to immediate breast reconstruction. In the absence of medical contraindications, women were offered a choice of breast preservation or mastectomy with or without immediate reconstruction and given the opportunity for preoperative consultation with a radiation oncologist or reconstructive surgeon.

The mean age of the young patient group was 36 compared with 46 for the older women. Differences in both medical eligibility for breast preservation and patient selection of type of local therapy were noted between the two age groups. Five of

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the 42 women age 40 or younger had stage III or IV breast carcinoma and are excluded from the analysis of choice of local therapy, as was a single patient presenting with axillary adenopathy and an occult primary tumor. Of the remainder, 37% were not felt to be candidates for breast-conserving therapy. The most common contraindication to breast preservation in the 40 and under group was the inability to achieve negative margins, which occurred in six cases. In five of the six, an extensive intraductal component was present. Large tumor size relative to breast size occurred in four cases (range, 3-9 cm), and in two cases multiple primary tumors were present. Only 25% of women over 40 with stage 0, I, and II cancer were found to have medical contraindications to breast preservation, primarily diffuse microcalcifications and an inability to obtain negative margins. No patients had contraindications to immediate breast reconstruction. These data are summarized in Table 1.

The treatment choices of the women who had no contraindications to breast preservation are listed in Table 1. A higher proportion of women in the under 40 age group (21% versus 9%) opted for mastectomy with reconstruction when compared with their older counterparts. Conversely, more women in the over 40 age group selected lumpectomy, axillary dissection, and radiotherapy as a local treatment modality. The importance of maintaining a breast is emphasized by the fact that only 4% of women in either age group underwent mastectomy alone after being informed in their treatment choices. Comparison data are difficult to obtain, since the majority of reports (5-12,15-20) deal with women selected on the basis of the treatment they received. Data from the National Cancer Data Base (14) indicate that in 1990, fewer than one-half of women with early-stage breast cancer underwent breast conservation. The percentage of women retaining their breasts ranged from 20.6% in the west south central area of the country to a high of 55.1% in New England. However, operative procedure was not analyzed by age, and it is not clear whether the low breast-preservation rates are due to physician bias, patient preference, or a combination of both.

The data presented here emphasize several important points regarding the local therapy of breast cancer in young women. Although mammographically detected carcinomas are infrequently seen in women under 40 due to the lack of screening in this age group, mammography provides valuable information

for treatment planning in women considering breast preservation. High-quality mammography, including compression and magnification views, is essential prior to biopsy to determine eligibility for breast-conserving procedures.

The overwhelming preference of these women to maintain a breast, either by lumpectomy and radiotherapy or breast reconstruction, raises additional questions. Are the outcomes of these procedures the same in young women as their older counterparts? The available data on outcomes and morbidity with respect to age will be reviewed below.

Local Failure After Breast-Conserving Surgery in Younger Women

The role of age as a determinant of local recurrence after breast-conserving surgery was first questioned by Vilcoq et al. (7) in 1981. In a retrospective review of 314 women treated at the Institute Curie by lumpectomy and radiotherapy, they observed a 35% incidence of local failure at 3 years in 20 women less than 30 years of age, compared with a 0% incidence in women over 50. A more detailed follow-up study from the Institute Curie (8) of factors influencing local failure after breast-conserving surgery found age to be the most important predictor of local control. This study, which included 518 women treated between 1960 and 1980, with a median follow-up of 8.6 years, reported a 10-year actuarial breast recurrence rate of 29% for women 32 years of age or younger ($n = 35$), compared with 15% for women aged 33-45, 6% for women aged 46-55, and 3% for women older than 55 ($P < .0001$). In a multivariate analysis of clinical and pathologic variables, young patient age, the presence of gross tumor at the margin of resection, and intralymphatic tumor spread were the three factors most predictive of local failure. Kurtz et al. (9) found that age did not influence local failure when 50 was used as a cut-off point, but the incidence of breast recurrence at 5 years was 12.1% in women under 40 compared with 5.8% in women aged 40 or above (10). This difference could not be explained by clinical factors. Young patient age was also found to correlate with local failure in reports from the M. D. Anderson Hospital (11) and the Joint Center for Radiotherapy (12). In reviewing the experience from the Joint Center, Boyages et al. (12) noted a 25% incidence of breast recurrence at 5 years in 61 women less than 35 years of age, compared with an 11% recurrence rate in 722 women aged 35 or older ($P = .001$). Some of this difference was attributed to the fact that extensive intraductal carcinoma, a factor previously shown to correlate with an increased risk of local recurrence (15), was more frequent in the younger group of women. However, a significant increase in the incidence of local failure was observed in women under age 34 compared to those 35 or older, even when those with extensive intraductal cancer were excluded from analysis (22% local recurrence \leq age 34 versus 3% local recurrence \geq age 35; $P = .0003$).

These data would seem to clearly indicate that age is a significant predictor for local failure. However, the studies discussed generally base their conclusions on small numbers of patients treated by gross tumorectomy, with no attention to margin status. The absence of histologic nodal staging and information on the use of adjuvant chemotherapy or hormonal therapy

Table 1. Choice of operative procedure—stage 0, I, II

	Age, y	
	≤ 40	≤ 50
Ineligible for conservation	37%	25%
No. of patients with multiple primary tumors	2	3
No. of patients with diffuse microcalcifications	1	5
No. of patients with positive margins/EIC*	6/5	5/2
No. of patients with large tumor-to-breast ratio	4	2
No. of noncompliant patients	1	0
Eligible for conservation		
Breast preservation	75%	87%
Mastectomy + reconstruction	21%	9%
Mastectomy	4%	4%

*EIC = extensive intraductal component.

make it difficult to evaluate the relevance of these findings to current practice. However, a study by Veronesi et al. (16), employing quadrantectomy, axillary dissection, standardized radiotherapy, and adjuvant chemotherapy for all patients with positive nodes, found a 6% incidence of local recurrence in women 35 and younger compared with a 3% local failure rate for those over 35.

A number of other studies have failed to substantiate patient age as an important predictor for local recurrence after lumpectomy and radiotherapy. Clarke et al. (17), in a report of 436 women treated at the Institute Gustave Roussy between 1970 and 1981, failed to observe a significant difference in local failure rates at 5 years between women aged 35 and younger and their older counterparts. Van Limbergen et al. (18) found that age less than 40 was a predictor of local recurrence in univariate analysis, but did not remain significant in a multivariate analysis. Solin et al. (19) reviewed the University of Pennsylvania experience from 1977 to 1986. Their series included 88 women less than 36 years of age and 808 older than 36 at the time of treatment. All patients underwent axillary dissection, and histologic margin assessment was available for 53% of the group. Re-excision was carried out in 64% of the younger women and in 49% of the older women prior to irradiation. Forty percent of the young women received chemotherapy compared with 22% of the older group. At 5 years no significant difference in the incidence of local failure between groups was observed. However, Solin et al. (19) did note that local failure occurred earlier in younger women than in their older counterparts. This difference was evident in the first 3 post-treatment years but had disappeared after 5 years of follow-up. Similarly, Kurtz et al. (10) observed a 12.1% incidence of breast recurrence in the first 5 years post-treatment in women under 40 compared with a 5.8% failure rate in older patients, but the annual risk of recurrence between 5 and 10 years post-treatment did not differ between age groups.

Kurtz et al. (20) evaluated 496 stage I and II breast cancer patients for clinical and pathologic predictors of local recurrence after conservative surgery and radiotherapy. Multivariate analysis demonstrated that mononuclear cell reaction and the presence of an extensive intraductal component were significant predictors of local failure. The incidence of each of these variables was strongly age dependent, with women under 40 having a significantly higher prevalence of each individual risk factor than women in older age groups. The crude 5-year local recurrence rate for women under 40 ($n = 62$) was 21%, compared with 11% for women in older age groups. However, when the women under 40 were stratified by the presence of histologic risk factors, only one local failure (3.1%) was seen in the 32 women with no risk factors compared to a 48% incidence of local failure for women with one or both risk factors. These findings led the authors to conclude that women at high risk for recurrence should be identified by morphologic features of the primary tumor rather than by age alone. Confirmation of the importance of tumor histology as a predictor of local failure is found in the work of Vicini et al. (21). The presence of an extensive intraductal component was found to be a predictor of an increased incidence of local failure. However, for extensive intraductal component-positive patients the incidence of local

failure was decreased as the size of the surgical resection increased. In women with extensive intraductal component-negative tumors, low rates of local recurrence were observed, regardless of the amount of breast tissue resected. Harris et al. (15) and Kurtz et al. (20) have both demonstrated that an extensive intraductal component is more common in younger women. These observations, coupled with the low local failure rate (6%) reported after quadrantectomy in young women (16), suggest that wider surgical resection for young women at increased risk for local failure on the basis of tumor morphology could reduce local recurrence rates. In addition, differences in the extent of breast resection, as well as differing proportions of women with an extensive intraductal component, could account for the wide range of local recurrence rates noted in Tables 2 and 3.

Evidence that histologic features of the primary tumor may be responsible for an increased risk of local failure after breast preservation raises the intriguing question of whether younger women may also be at increased risk for local recurrence after mastectomy. Matthews et al. (11) observed increased rates of local failure in women 35 or younger undergoing mastectomy or breast preservation for the treatment of stage I and II cancer. Local failure rates after mastectomy decreased from 12% in women 35 or younger to 5.5% for women aged 36-50. A similar increase in local failure rates after mastectomy in younger women was reported by Donegan et al. (22). However, many of the patients in this report had locally advanced breast cancers, and cases were not stratified by nodal status or by clinical stage.

At present, it is not possible to definitively state whether young women have an increased risk of local failure after breast-preserving surgery, and if such risk exists, whether it is due to age, histologic factors, or an interaction between these variables. Local recurrence in the breast in young women does not seem to result in a decrease in survival (10,12), a finding consistent with the results of randomized trials of breast-conserving surgery (5,6). In light of this, young patient age should not be considered a contraindication to breast preservation at this time.

Table 2. Age and local recurrence: positive studies

Authors (ref. No.)	Age cutoff, y	No. of young patients	% recurrence	Follow-up, mo
Vilcoq et al. (7)	≤ 30	20	35	>36
Kurtz et al. (10)	<40	210	12.1	132 (median)
Boyages et al. (12)	≤ 34	53	25	80 (median)
Veronesi et al. (16)	≤ 35	95	6.3	72 (median)
Clark et al. (17)	≤ 45	43	18	60
Stotter et al. (24)	≤ 50	Not stated	11	64 (median)

Table 3. Age and local recurrence: negative studies

Authors (ref. No.)	Age cutoff, y	No. of young patients	% recurrence	Follow-up, mo
Clarke et al. (17)	<35	32	5	60
Van Limbergen et al. (18)	<40	Not stated	21	97
Solin et al. (19)	≤ 35	88	7	40
Kurtz et al. (20)	<40	62	21	71 (median)

A final consideration when evaluating the incidence of local failure in young women is the effect of adjuvant chemotherapy or hormonal therapy on the risk of recurrence in the breast. Randomized trials from the National Surgical Adjuvant Breast Project (5,25,26) indicate that the use of adjuvant therapy decreases the rate of local failure in the breast in both node-positive and node-negative women. The increasing trend toward the use of adjuvant chemotherapy in node-negative premenopausal women may have a significant positive impact on the risk of local failure in younger women.

Morbidity of Local Therapy for Breast Cancer in Younger Women

Loss of the breast has been the most readily apparent morbidity of the local therapy for breast cancer. The increasing acceptance of breast-conserving surgery and immediate breast reconstruction as options for the treatment of early breast cancer should help ameliorate this problem in the future. However, there are important unanswered questions about the long-term cosmetic outcome of each of these procedures in young women. Cosmesis after breast-conserving surgery and radiotherapy has been extensively studied, and the appearance of the breast continues to change for the first 36 months after the completion of radiotherapy. After that interval, the cosmetic result has been shown to be stable over a follow-up period of 8 years (27). Less is known about the long-term cosmetic outcome of breast reconstruction. However, the number of women under age 40 in existing cosmesis studies is small and specific issues pertinent to young women undergoing breast conservation or reconstruction are not addressed. Pregnancy, changes in body weight, and the aging process are well known to affect the appearance of the normal breast. Although excellent breast symmetry can be achieved with breast-conserving approaches or modern reconstructive techniques, the long-term stability of the cosmetic result in young women is an area which requires further study.

The other major component of the local therapy of breast cancer, whether a mastectomy or breast conservation is undertaken, is axillary dissection. Lymphedema of the arm secondary to axillary dissection is the most significant functional morbidity that is seen after the local therapy for breast cancer. The incidence of lymphedema after axillary dissection ranges from 1.5 to 62.5% (28-33). This wide variation in incidence is explained by differences in the definition of lymphedema and techniques used to quantitate lymphedema, variation in the extent of axillary dissection, and differences in patient groups. Pezner et al. (29) found that age at diagnosis was a significant predictor of the risk of lymphedema of the arm in women after breast-preserving surgery and radiotherapy. Twenty-five percent of women over age 60 developed lymphedema compared with 7% of younger women ($P < .02$). In the younger women, obesity was associated with an increased risk of lymphedema. Other authors (28,34,35) have not found an association between patient age and the risk of lymphedema.

Although it is not clear whether the incidence of lymphedema is age related, women undergoing axillary dissection are at lifetime risk for the development of this problem (33), and studies with long-term follow-up report higher frequencies of

lymphedema (31,32), making this a particular concern for the young breast cancer patient with early-stage disease. A lifetime of precautions to prevent the development of lymphedema may impose significant restrictions on younger women accustomed to vigorous physical activity or those women whose occupation demands repetitive arm use. Other long-term complications of axillary dissection are as follows: shoulder dysfunction, anesthesia in the intercostobrachial nerve distribution, lymphedema of the arm, breast edema, and unsatisfactory cosmesis.

Due to the absence of reliable, noninvasive techniques for determining axillary node status, axillary dissection has remained a standard part of the local management of breast cancer. The recognition of the importance of axillary lymph node metastases as an indicator of decreased survival after breast cancer surgery (36,38) and clinical trials demonstrating a prolongation of survival for women with node-positive breast cancer treated with adjuvant chemotherapy or hormonal therapy (39-42) have mandated accurate axillary staging. However, the publication of several clinical studies (25,26,43) demonstrating an improvement in disease-free survival with the use of adjuvant therapy in node-negative breast cancer has resulted in a major change in the management of women with node-negative disease. Current recommendations for adjuvant therapy (44) emphasize treatment for both node-positive and node-negative women, and treatment recommendations are identical for both groups. If decisions about adjuvant therapy are no longer being made on the basis of axillary node status, then axillary dissection is necessary only to maintain local control in the axilla. In the absence of axillary adenopathy, radiotherapy has been shown to be as effective as surgical dissection in maintaining local control in the axilla (45-48). Thus, for the clinically node-negative women who opt for lumpectomy and radiotherapy and who will require adjuvant therapy on the basis of primary tumor factors, eliminating axillary dissection and extending the radiation field to cover the axilla are approaches that will decrease both the short-term and long-term morbidity of the local therapy of the breast cancer. Axillary dissection will continue to be necessary for women who undergo mastectomy, who have palpable axillary nodes or who are potential participants in clinical trials. In patients who would not receive adjuvant therapy unless positive axillary nodes are identified, axillary dissection remains an important staging procedure. In cases where axillary dissection is necessary, morbidity can be minimized by the use of appropriate surgical techniques. Avoiding dissection superior to the axillary vein and "stripping" of the vein with destruction of collateral lymphatic channels will help to decrease the risk of lymphedema of the arm. In the absence of clinically suspicious axillary adenopathy, the intercostobrachial nerve can be dissected free from the axillary fat pad, resulting in preservation of sensation in the upper inner aspect of the arm.

Conclusions and Recommendations

It is clear that an operative procedure in which the breast is maintained is the preference of more than 90% of young women. The increased use of prebiopsy mammography and aspiration cytology as a diagnostic technique will provide the necessary information to evaluate a woman's suitability for

breast conservation. Cosmetic outcome will be optimized if diagnostic biopsies are done as lumpectomies with evaluation of margins.

Whether young women treated with breast conservation are at increased risk of local failure compared with their older counterparts cannot be conclusively determined from the available data. A prospective trial that includes information on margin status, histologic tumor features, width of excision, and the use of adjuvant therapy is necessary to definitively answer this important question. In addition, studies of the long-term cosmetic outcome of breast preservation and breast reconstruction in young women will provide information needed to counsel these patients regarding treatment choices.

Finally, the need for routine axillary dissection must be re-evaluated in light of changes in our approach to adjuvant chemotherapy. A policy of selective axillary dissection would reduce the morbidity of breast cancer therapy. If our ability to tailor adjuvant therapy to an individual patient's needs improves, axillary dissection may again become necessary for all women. At present, it represents a cause of morbidity which does not alter therapy for many young women.

Our understanding of the biology of breast cancer has changed dramatically since many of the techniques used in breast cancer surgery were described. It is important that we continue to re-evaluate the components of local therapy in light of these changes, in an effort to minimize surgical morbidity without a decrease in local control rates or survival.

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Menstrual Timing of Treatment for Breast Cancer

Ruby T. Senie, David W. Kinne*

Although the hormone dependency of breast cancer has been recognized for nearly a century, the influence on disease progression of cyclical hormonal levels among premenopausal women has not been extensively researched. The findings of recent studies, assessing the effect on prognosis of the hormonal milieu at the time of surgery, have been conflicting. However, several reports have noted improved survival among patients with positive, axillary lymph nodes surgically treated in the later phase of the menstrual cycle when progesterone levels are elevated. Biologic support for the influence of menstrual timing is provided by cyclical patterns of cell division and cell death observed in normal breast tissue as well as potential tumor cell dissemination during surgery among patients with positive axillary nodes. Immune parameters, which also respond to cycling endogenous hormones, may influence the metastatic potential of circulating tumor cells. Comparisons among studies of menstrual timing of surgery have been complicated by differences in cycle divisions, extent of primary surgery, frequency of adjuvant therapy, duration of follow-up, and analytic procedures. Although several clinicians are now scheduling breast surgery of premenopausal women in relation to day of the menstrual cycle, a majority of surgeons have deferred consideration of menstrual timing until additional research is available. While waiting 5-10 years for the results of prospective studies, additional retrospective analyses, using carefully collected data, may provide clinical guidance. With increasing concern for issues related to women's health, multidisciplinary studies will be required to adequately characterize the influence of the menstrual cycle and other aspects of women's reproductive physiology on breast cancer and other medical conditions. [Monogr Natl Cancer Inst 16:85-90, 1994]

Although Beatson (1) demonstrated the hormone dependency of breast cancer in 1896 by achieving remission of disease through bilateral oophorectomy, the influence of cyclical, endogenous hormonal levels on breast cancer prognosis among premenopausal women has not been extensively researched. Interest in the effect of the hormonal milieu at the time of breast cancer treatment was stimulated by the 1989 publication of Hrushesky et al. (2).

After observing a prognostic effect of the timing of mammary carcinoma excisions during the estrus cycle among laboratory animals (3), these investigators were encouraged to assess the

influence on survival of the hormonal milieu at time of breast cancer treatment of women (2). Among 41 patients, significantly better survival was observed when surgery had occurred between days 7 and 20 (midcycle) in contrast to surgery during the perimenstrual interval (2). An additional study of 40 breast cancer patients conducted by Spratt et al. (4) reported a similar survival benefit ($P < .06$) in relation to these menstrual cycle intervals. However, several other investigators were unable to confirm these results (5-11). Rageth et al. (8) found no association between these cycle intervals and disease-free or overall survival among 271 patients. These authors, however, noted the frequency of positive nodes differed significantly by timing of surgery: 38% of patients treated in midcycle and 57% with perimenstrual timing of surgery. They suggested that cycling hormones may influence detectability of axillary lymph node metastases without influencing survival.

Other menstrual cycle divisions, based on hormone profiles, have been assessed by several researchers. Badwe et al. (12) contrasted days 3 through 12, an interval of unopposed estrogens, with days 0-2 and 13-32 when estrogen and progesterone levels were similarly stimulated. In this population of 249 patients, the proportion with recurrent disease was significantly greater (46%) when surgery had occurred between days 3 and 12, compared to 16% who relapsed following surgery at other times of the cycle ($P < .001$). The impact of timing was confined to patients with positive axillary lymph nodes. In a second series of patients with shorter follow-up, these investigators again observed significant survival differences associated with timing of surgery (13). However, results of several other studies did not confirm these findings. Gnant et al. (14) found no difference in survival among 192 patients with positive nodes. Among 143 patients, survival differences in the opposite direction were found by Sainsburg et al. (15); surgery on days 3-12 was associated with improved prognosis ($P = .03$), although multivariate analysis indicated timing was not an independent prognostic factor. Oral contraceptive use by more than 50% of these patients may have influenced results. Several other researchers with differing numbers of patients and less detailed

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See "Note" section following "References."

analyses found no significant impact of this menstrual cycle division on prognosis (11,16-19).

The third cycle division was based on the hormone-dependent phases determined by setting the 14th day after onset of menses as the putative day of ovulation (20). The follicular phase, before ovulation, is characterized by a rise and fall of estrogen in the absence of progesterone; after ovulation, estrogen levels again increase accompanied by a rapid rise in progesterone. Survival in relation to surgery during the follicular or luteal phase was assessed in several reports with conflicting results (4,8,9,11). A statistically significant, increased risk of recurrence during 10 years of follow-up was observed by Senie et al. (9) only among positive node patients with tumor excision during the follicular phase compared with the luteal phase (hazard ratio = 2.1). In contrast, Rageth et al. (8) reported no difference in disease-free or overall survival among the 271 patients by the follicular or luteal phase, although analyses stratified by nodal status were not performed. Survival at 7 years among 30 patients treated during the follicular phase in the study by Spratt et al. (4) was 64% compared to 86% among 10 women whose surgery occurred during the luteal phase. Although life table analysis in this report was extended to 10 years, the proportion of patients censored after 7 years was too high for meaningful assessment. The only study in which endogenous hormone levels were used to categorize premenopausal patients was conducted by Ville et al. (21); four divisions of the menstrual cycle were created (perimenstrual, follicular, ovulatory, or luteal) based on blood levels of progesterone, estradiol, and luteotropin assessed the day before surgery. Although that report did not include Kaplan-Meier curves to show no differences in survival, their published table noted fewer recurrences among patients treated during the luteal phase (21).

A fourth cycle division was used by Saad et al. (22); primary surgery on days 1-12 was compared to surgery on days 13-36 among 96 patients (22). Surgery late in the cycle was associated with significantly greater disease-free survival (75%) in contrast

to surgery during the first 12 days (40%); the effect was greatest among patients with positive nodes ($P < .01$).

Comparisons Among Studies of Menstrual Cycle Timing

Table 1 presents several published reports with adequate data to assess survival following surgery early in the menstrual cycle (days 0-12, 3-12, and follicular phase) or later (luteal phase, days 0-2, and days 13-36). Four reports indicated significant differences in prognosis related to timing of surgery; a trend was noted in an additional study. Although multivariate analyses were conducted by some authors, analyses stratified by nodal status were not routinely performed. Several additional studies published as letters are not listed in Table 1 because of inadequate data for appropriate comparisons.

A meta-analysis combining data from 10 published reports (23) revealed a significant overall effect of the timing of surgery ($P = .003$); however, the value of the summary statistic was diminished by the inclusion of studies with very different methodologies. The concordance among three similarly designed investigations, in which surgery early in the menstrual cycle had a significantly adverse effect on disease-free survival only among positive node patients, encourages continued assessment of the prognostic effect of the timing of surgery.

Comparisons among studies are hampered by differences in: divisions of the menstrual cycle, source and characteristics of study population, interval of patient accrual, primary and adjuvant treatment, stage of disease at diagnosis, duration and completeness of follow-up, and analytic methodology.

Menstrual Cycle Divisions

The initial menstrual cycle division, based on animal research (3), was less appropriate than approximating the recognized menstrual cycle phases documented through extensive studies of female hormone profiles (20). Fig. 1 notes that three of the four

Table 1. Menstrual cycle timing of breast cancer surgery and survival*

Author (ref. No.)	Years of accrual	% with LMP data	Sample size	Follow-up interval, y	Overall survival, %		Disease-free survival, %		Significance
					Follicular phase†	Luteal phase	Follicular phase†	Luteal phase	
Spratt et al. (4)	1972-1977	Not stated	40	7	64	86	Not stated	Not stated	Not stated
Rageth et al. (8)	1971-1988	71	217	5	82	80	55‡	46	Not significant
Senie et al. (9)	1976-1978	90	283	10	67	82	57	71	$P = .02$
Badwe et al. (12)	1975-1985	44	249	9	54	84	42‡	75‡	$P < .001$
Badwe et al. (13)	1985-1990	Not stated	150	Not stated	Not stated	Not stated	38‡	70‡	$P = .001$
Gnant et al. (14)	1977-1989	56	385	5	83	80	70	72	Not significant
Sainsbury et al. (15)	Not stated	42	143	10	70‡	48‡	Not stated	Not stated	$P = .06$
Nathan et al. (16)	1979-1988	58	132	Not stated	58‡	54‡	Not stated	Not stated	Not significant
Goldhirsch et al. (17)	Not stated	Not stated	225	10	65	55	54	44	Not significant
Powles et al. (18)									
RM	Not stated	Not stated	205	11	60‡	62‡	Not stated	Not stated	Not significant
StG			108		65‡	74‡			
Low et al. (19)	1974-1986	30	125	Not stated	56‡	58‡	45‡	55‡	Not significant
Saad et al. (22)	1975-1988	30	86	10	39	74	40	75	$P = .01$

*RM = Royal Marsden series; StG = St. George series; LMP = last menstrual cycle.

†Follicular phase: days 0-12, 3-12, 0-14.

‡Estimate from survival curve.

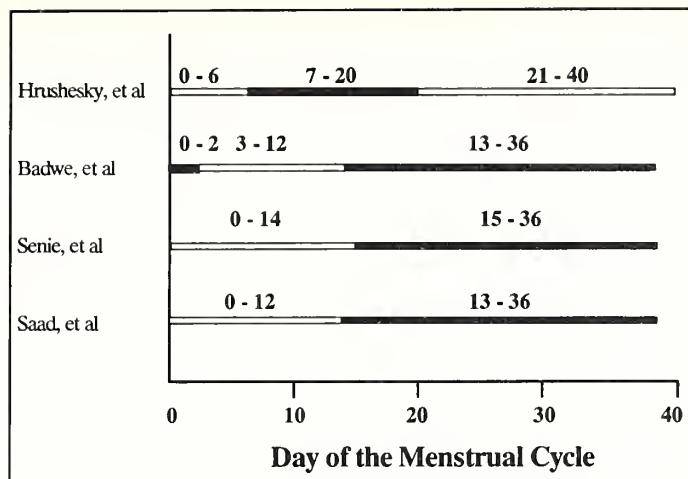


Fig. 1. Menstrual cycle divisions included in published studies of the prognostic effect of timing of surgery.

menstrual divisions greatly overlap, although they differ considerably from the initial scheme of Hrushesky et al. (3). Future studies must not rely on recalled dates of last menses and on usual cycle length. To avoid misclassification of menstrual phase, serum specimens should be obtained for assessment of the hormonal milieu at time of surgery (9,24,25).

Patient Characteristics

Differing characteristics of the study subjects also complicate comparisons. Some studies included women from multiple institutions who were enrolled in adjuvant clinical trials (6,17), while others were case series from single or affiliated institutions (4,9-13). Exclusion of women reporting recent hormone use or pregnancy was not consistently noted. Stage of disease also differed considerably. In addition, sample sizes were frequently small and were restricted, primarily by lack of data on last menstrual period that limited the power to detect significant results (Table 1). Several reports included study patients with positive nodes and advanced disease, while others were confined to patients with earlier diagnosis. Because several studies observed survival differences only among positive node patients, subset analyses should be consistently performed.

Primary and Adjuvant Treatment

Primary surgical treatment has evolved over the years of patient accrual among the timing studies. In the late 1970s, breast cancer surgery consisted of biopsy confirming the diagnosis followed by mastectomy and axillary dissection as a single surgical procedure; more recently, multiple surgical procedures are frequently performed. For consistency, several authors have studied the timing of *first* surgical intervention, regardless of the total number of procedures; the impact of the timing of multiple procedures on survival remains to be assessed. The frequency of adjuvant chemotherapy and radiation therapy also differs significantly among studies. Multivariate survival analyses using the Cox proportional hazards regression procedure provide a means for controlling differences in treatment; however, this statistical methodology was not uniformly applied.

Duration and Completeness of Follow-up

The duration and completeness of follow-up also differed considerably among the publications. Although median follow-up intervals extended from 5 to 11 years, some study subjects were treated within 2 or 3 years of analysis. The low number of recurrences or deaths expected during limited follow-up intervals may have reduced the probability of detecting a true prognostic effect.

Analytic Methodology

The quantity of data included in published timing studies varies greatly, hampering comparisons of study design and statistical methodology. However, several research groups with appropriately described methodology revealed similar results after applying multivariate analytic methods. The number of incompletely described published analyses increased concerns for chance detection of statistically significant findings that complicate all research endeavors. To address this issue, McGuire et al. (24) created a simulated study by randomly assigning a date of last menses to the patient histories included in their large database that emphasized the need for a prospective, carefully designed investigation.

Menstrual Cycle Variability

Studies involving the menstrual cycle are complicated by the considerable variability women report in relation to age, reproductive history, medical conditions, psychosocial experiences, and other factors (26,27). However, extensive cohort studies have indicated that a majority of women experience regular cycles, averaging 28 days during most of their menstruating years (27). More research is required to adequately characterize the influence of cyclical hormonal patterns on women's health, especially the effect on hormone-dependent conditions.

Influences of Menstrual Cycle on Breast Tissue

Studies of normal breast tissue have revealed changes in breast size, texture, and sensitivity during the menstrual cycle that have been frequently reported by women in relation to the cyclical hormonal milieu of the menstrual cycle. Among several factors studied are breast volume (28-30), histologic changes including cell division and cell death (31-33), thymidine-labeling index (34,35), estrogen and progesterone receptor levels (36-39), and immune parameters including natural killer (NK) cells (40,41).

Variations in breast volume and sensitivity during the menstrual cycle have been reported and measured by several researchers (28-30). Magnetic resonance imaging (MRI) documented marked increases in total breast and parenchymal volumes as well as water content in the latter phase of the cycle following ovulation (30). These findings correspond to those reported by others, using more conventional measurement techniques (28,29). Drife (28) suggested the cyclical changes in the breast may be linked to malignant transformation.

Using thymidine-labeling index techniques, several investigators have documented the biorhythm of cell division and cell

deletion in the breast tissue of normal women, corresponding to the shifting hormonal milieu of the menstrual cycle; rates of mitosis and apoptosis decreased with age at time of breast biopsy and were altered by exposure to exogenous hormones (31,32). Others (33-35) have observed menstrual cycle-dependent histologic patterns in epithelium and stroma of normal breast tissue.

Conflicting results have been reported when estrogen and progesterone receptors were studied in relation to phase of the menstrual cycle at time of tumor excision. Several reports found no significant association of receptor levels with menstrual cycle phase at the time of tumor excision (36,38,39), while others found increasing mean concentrations during the luteal phase (37). These conflicting findings may reflect differences in hormonal patterns associated with age at diagnosis.

Lowered immune parameters observed during the follicular phase associated with rising levels of unopposed estrogens may potentiate metastatic spread at the time of tumor excision. Some investigators have reported that NK cell activity falls significantly before ovulation among premenopausal breast cancer patients and healthy women (40,41). Interleukin 1 secretion from cultured monocytes was found to increase with luteal phase concentrations of progesterone (42), and a significant decrease in phagocytic activity of mononuclear cells early in the menstrual cycle was reported by Stratton et al. (43). Mice treated with β -estradiol exhibited lower NK cell activity and enhanced susceptibility to metastases (44). Thus, the diminished NK levels associated with the follicular phase may be further compromised following surgery early in the menstrual cycle, resulting in reduced host resistance to seeding of metastases by circulating tumor cells.

Influences of Menstrual Cycle on Mammary Tumor Cells

Ervin, Wicha, et al. (45,46) noted that mammostatin, a protein produced by normal human mammary cells, controls cell proliferation. Decreased production of mammostatin by transformed compared with normal mammary cells may contribute to the loss of growth control associated with malignancy. Mammostatin levels were found to correspond to the hormonal milieu of the menstrual cycle (46).

In vitro studies revealed an increase in the growth fraction (GF) of human breast adenocarcinomas in the presence of estrogen; however, when both estrogen and progesterone were present, GF was significantly depressed regardless of receptor status (47). Other investigations of human breast cancer cells noted the antiproliferative activity of progesterone, independent of estrogen, suggesting progestin therapy may retard tumor growth (48,49). These studies support the hypothesis that elevated estrogen levels unopposed by progesterone at the time of surgery during the follicular phase may enhance the growth of circulating cancer cells in patients with positive axillary nodes who have a higher probability of metastatic seeding. McGuire (50) suggested a short course of tamoxifen might be administered before surgery, if additional research convincingly demonstrates the effect of timing. Some clinicians have proposed progesterone administration at the time of surgery to

simulate the luteal phase may enhance prognosis (Holland J: personal communication).

Potential Biologic Mechanisms

Endogenous hormones may influence the growth and metastatic potential of tumor cells released into the bloodstream during surgery (51). Concern for the risk of surgery-induced tumor cell dissemination led to the initiation of one of the earliest adjuvant chemotherapy protocols in which a short course of thiotepa was administered perioperatively (52). Treated patients had a significant survival advantage compared with controls during 10 years of follow-up; however, the effect was limited to premenopausal patients with positive axillary nodes (52). In a large Scandinavian study (53), 20 years after breast cancer diagnosis, a short course of chemotherapy immediately after surgery was associated with a significantly reduced risk of recurrence, especially among node-positive patients. Although some studies have found short-term chemotherapy inadequate and favor initiation of systemic therapy several weeks after surgery (54), renewed interest in perioperative treatment has been expressed (55). One potential mechanism of action on menstrual timing for breast surgery may be the influences of the hormonal milieu on perioperative seeding of metastases.

Some gynecologists have hypothesized that surgery during the follicular phase may delay ovulation, lengthening the interval during which the growth of circulating cancer cells may be enhanced by unopposed estrogens. This theory is supported by Soules et al. (56), who observed reduced progesterone levels during the luteal phase in patients following surgery under general anesthesia. They suggested that ovarian steroid production was temporarily compromised by the toxic effect of general anesthesia (56). Further studies are needed to assess the influence that general anesthesia has on menstrual cycle patterns. An additional hormonal influence of surgery was reported by Barni et al. (57), who found postoperative prolactin levels varied with the phase of the menstrual cycle at time of surgery; high prolactin levels have been associated with poor prognosis.

Therefore, several potential biologic mechanisms associated with breast cancer prognosis may be related to the timing of tumor excision and possibly subsequent surgery, especially in those with positive node axillary lymph nodes. Further research must include biochemical assessment of menstrual phase at the time of surgery and determination of the interval between last preoperative and first postoperative menses to appropriately categorize study subjects.

Future Research

Several investigators have called for prospective studies to address many of the issues uncontrolled in the retrospective comparisons, using data collected for unrelated analyses (2,9,24). Retrospective analyses may be biased because of the inconsistency of menstrual cycle information recorded in medical charts among several studies listed previously. Although a randomized clinical trial has become the standard, the complexity of scheduling randomly allocated patients, with unconfirmed stage of disease, could jeopardize the investigation.

Ethical issues must also be considered, and informed consent may be difficult to obtain (58). Several prospective, observational studies are under way, which may clarify some of the relationships between the hormonal milieu at time of surgery and disease progression, including a multicenter study (59) in England and an institution-based study (Zhida S: personal communication) in Canada.

Although several clinicians are now scheduling breast surgery on premenopausal women in relation to day of the menstrual cycle, a majority of surgeons have deferred consideration of menstrual timing until additional research is available. Prospective studies may be optimal to clarify the suggested relationships; however, additional retrospective analyses, using carefully collected data, may provide clinical guidance while waiting for results during the 5-10 years of follow-up.

Menstrual Timing of Other Aspects of Breast Cancer Care

Concern with timing during the menstrual cycle may influence other aspects of breast cancer care, including the scheduling of screening and chemotherapy. In recognition of changes in breast tissue corresponding to the estrogen-progesterone sequence of the menstrual cycle, some gynecologists advise breast examinations during the follicular phase when breast tissue is softest (60). Similarly, premenopausal women enrolled in the Canadian National Breast Screening Study were advised to schedule their appointments the week after onset of menses (Baines C: personal communication). Consensus on this recommendation was not evident in a limited survey of mammographic centers in New York City. Only one private facility specifically stated that a mammogram would be easier to read and the procedure more comfortable if performed shortly after menses; no specific interval was indicated by the other centers contacted.

Menstrual timing of systemic therapy received little interest until a recent report by Whitaker et al. (61). These investigators observed reduced fertility when cytotoxic chemotherapy was administered to laboratory animals at a time of rapid follicular cell division during the estrus cycle. An additional question may be related to the potential effect of menstrual timing of systemic therapy on drug tolerance and immediate side effects.

As interest and concern for women's health increase, multidisciplinary studies should be conducted to adequately characterize the influence of the menstrual cycle and other aspects of women's reproductive physiology on health and disease, including breast cancer.

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Note

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High-Dose Cyclophosphamide, Thiotepa, and Carboplatin With Autologous Marrow Support in Women With Measurable Advanced Breast Cancer Responding to Standard-Dose Therapy: Analysis by Age

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The analysis was undertaken to determine if the time to progression and survival for women with breast cancer treated with high-dose chemotherapy after a conventional-dose induction therapy differs significantly for women younger and older than 40 years of age. All patients treated in phase II or III protocols of high-dose chemotherapy for breast cancer are included in this analysis. Women were treated on one of six protocols: four sequential phase II protocols for metastatic breast cancer involving cyclophosphamide at a dose of 6000 mg/m², thiotepa at 500 mg/m², and carboplatin at 800 mg/m² (CTCb) chemotherapy; one phase II study of CTCb chemotherapy for stage III or inflammatory breast cancer; and a Cancer and Leukemia Group B phase III study of cyclophosphamide, carmustine, and cisplatin for women with more than 10 involved lymph nodes after primary therapy. Eligibility criteria for the patients with metastatic disease included histologically documented breast cancer, at least a partial response to conventional dose therapy, no prior pelvic radiotherapy, cumulative doxorubicin of less than 500 mg/m², and physiologic age of 18-55 years. Patients with inadequate renal, hepatic, pulmonary, and cardiac function or tumor involvement of marrow or central nervous system were excluded. Of 99 registered patients, three (3%) died of toxicity. There were no toxic deaths in protocols for stage II and III disease, and to date none of these patients have relapsed. Thus, there are no differences by age for these studies. In patients treated for metastatic disease, there is significantly shorter disease-free ($P = .03$) and overall survival ($P = .03$) for patients younger than age 40 compared to older patients. No differences were observed by age in women receiving high-dose chemotherapy for stage II and III disease, but numbers were small and follow-up was short. [Monogr Natl Cancer Inst 16:91-94, 1994]

Breast cancer currently develops in 10% of American women. Metastatic breast cancer is essentially incurable, with a median survival with conventional dose therapy of about 2 years after documentation of metastases (1,2). Subsets of patients with

primary breast cancer, specifically those with many involved lymph nodes or locally advanced (stage III) disease, also have a high probability of dying of disease within a decade. In laboratory models of breast cancer, administration of the highest possible doses of chemotherapy is essential to the design of curative regimens (3).

The objective of the Dana-Farber Cancer Institute/Beth Israel Hospital (DFCI/BIH) clinical program was to develop a high-dose combination regimen with a low mortality and significant activity in breast cancer for use in women with a poor prognosis with conventional-dose therapy.

Chemotherapy with the combination of cyclophosphamide, thiotepa, and carboplatin (CTCb) proved active against measurable metastatic disease (4). Although myelosuppression was profound, significant nonhematopoietic toxicity was uncommon. An analysis was undertaken to determine if younger women participating in this program had a prognosis different from older women.

Methods

Patient Selection

All women treated on DFCI/BIH phase II or III protocols of high-dose chemotherapy for breast cancer are included in this analysis. Women were treated on one of six protocols: four sequential phase II protocols for metastatic breast cancer involving cyclophosphamide at a dose of 6000 mg/m², thiotepa at 500 mg/m², and carboplatin at 800 mg/m² (CTCb) chemotherapy; one phase II study of CTCb chemotherapy for stage III or inflammatory breast cancer; and a Cancer and Leukemia Group B phase III study of cyclophosphamide, carmustine, and cisplatin

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See "Notes" section following "References."

for women with more than 10 involved lymph nodes after primary therapy. Eligibility criteria for all patients included adequate renal, hepatic, pulmonary, and cardiac function and no prior pelvic radiotherapy. For patients with metastatic disease, histologically documented breast cancer, at least a partial response to conventional-dose therapy, cumulative doxorubicin <500 mg/m², and physiologic age of 18-55 years were required. Patients with tumor involvement of marrow or central nervous system were excluded.

Supportive Care and Bone Marrow Reinfusion

The techniques of bone marrow harvest under general anesthesia, cryopreservation and reinfusion, and supportive care have been previously reported (5,6).

Statistical Methods

Lesions were measured prior to the initiation of chemotherapy. Palpable tumors and those visible on chest roentgenogram were measured weekly. More complicated imaging studies were delayed until reverse isolation was discontinued. Standard response criteria were used. Complete response (CR) or partial response (PR) were defined as the disappearance of all tumor, or a 50%-99% reduction in the product of the bidimensional measurements, respectively, for a minimum of 4 weeks. PR (bone scan positive) included the subset of patients who had complete resolution of all soft-tissue disease and sclerosis of prior lytic bone lesions but continuing activity by bone scan in areas of prior uptake. Disease progression was defined as a greater than 25% increase in tumor size or the appearance of any new lesions. Patients who died early of toxicity were considered unassessable for response, although tumor progression was coded if observed.

Data were pooled from the four studies using the CTCb regimen in stage IV patients to generate the curves for metastatic disease and from the two studies in women with 10 or more involved lymph nodes and in those with stage III and inflammatory breast cancer to generate curves for locally advanced disease. Survival and time to disease progression were calculated from the date of marrow reinfusion. Time to failure and survival were estimated by the Kaplan-Meier method (7). A multivariate analysis was not performed and currently would not be appropriate given the size of the database and the length of follow-up.

Results

Between May 1988 and February 1993, 99 women were entered on six DFCI/BIH studies. Study schemas are shown in Table 1.

Toxicity

Three patients (3%), all treated on protocols for stage IV disease, died while neutropenic (of central nervous system bleeding, congestive heart failure, and multiorgan failure, respectively).

Analysis by Age

There were no toxic deaths or relapses in patients treated on protocols for stage II and III disease. However, numbers are small and follow-up is short (Fig. 1).

Table 1. Study schemas

	Source of hematopoietic stem cells	Growth factor*	No. of patients
High-dose regimen			
<i>Stage IV responding to conventional dose induction regimen</i>			
Cyclophosphamide, thiotepa, carboplatin	Marrow	None	29
Cyclophosphamide, thiotepa, carboplatin	Blood	None	15
Cyclophosphamide, thiotepa, carboplatin	Blood	GM-CSF	18
Melphalan, then cyclophosphamide, thiotepa, carboplatin	Marrow and blood	G-CSF	20
<i>Stage III responding to 4 cycles of doxorubicin at 90 mg/m² every 14 days (with G-CSF)</i>			
Cyclophosphamide, thiotepa, carboplatin	Marrow and blood	G-CSF	10
<i>Stage II, >10 involved lymph nodes</i>			
Cyclophosphamide, carmustine, cisplatin	Marrow and blood	G-CSF	7

*GM-CSF = granulocyte-macrophage colony-stimulating factor; G-CSF = granulocyte colony-stimulating factor.

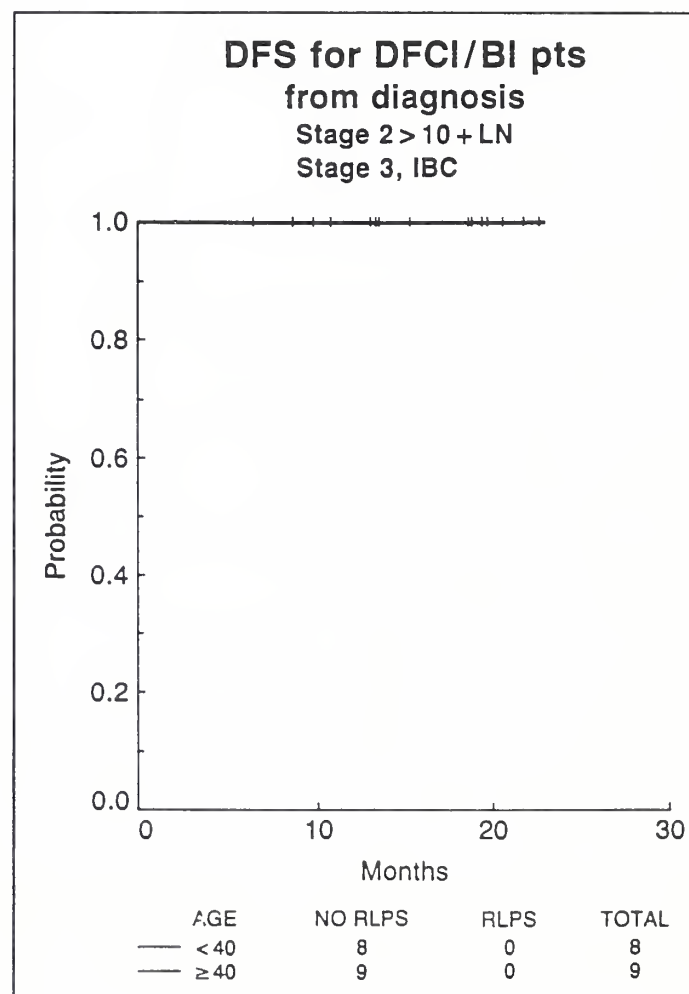
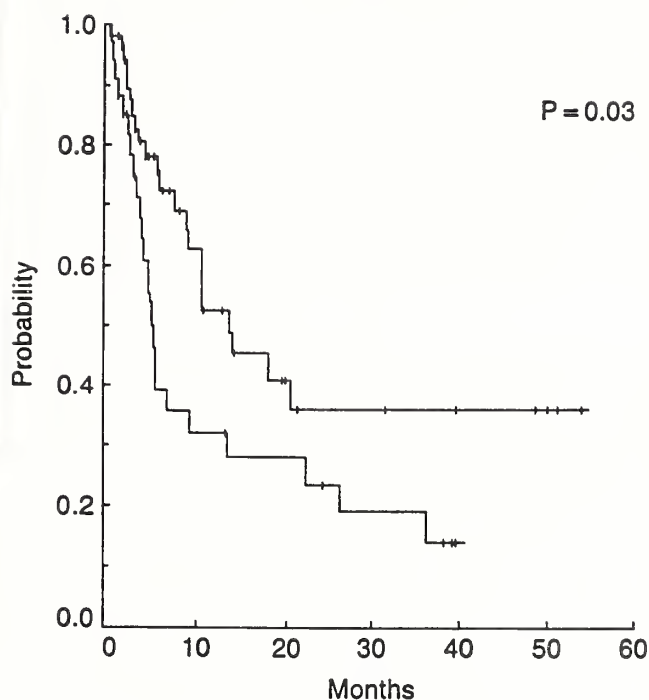


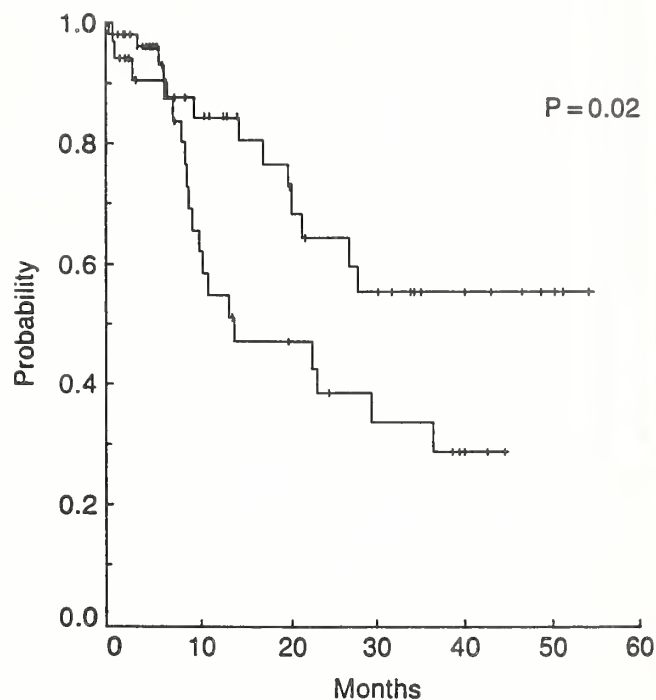
Fig. 1. The disease-free survival is shown for 17 women with stage II and III disease by age. There were no toxic deaths and no relapses to date.

DFS for DFCI/BI pts Responding Stage 4 N = 82



AGE	NO RLPS	RLPS	TOTAL	MEDIAN
<40	9	24	33	5
≥40	27	22	49	14

Survival DFCI/BI pts Responding Stage 4 N = 82



AGE	CNSR	DEATH	TOTAL	MEDIAN
<40	13	20	33	14
≥40	36	13	49	-

Fig. 2. The disease-free survival (left panel) and survival (right panel) are shown for 82 women with metastatic disease by age. Women less than 40 years old had a significantly shorter disease-free and overall survival.

Women under age 40 with metastatic breast cancer responding to conventional-dose induction therapy who underwent dose-intensive therapy with CTCb had significantly shorter disease-free ($P = .03$) and overall survival ($P = .02$) compared with those over age 40 (Fig. 2). Younger women had similar rates of CR, prior adjuvant chemotherapy, and adjuvant doxorubicin to older women. Thus, the reason for their poorer prognosis is not immediately apparent.

Discussion

The principles of dose-response and combination chemotherapy were basic to the design of treatment regimens for malignancies now curable with chemotherapy (e.g., leukemias, lymphomas, and testis and breast cancers in the adjuvant setting) (8-11). These strategies have been used to design high-dose regimens for use with hematopoietic stem cell support.

In our phase II studies, CTCb has proved to be an intensification regimen with a low mortality that achieves the goal of delivery of significantly increased doses of agents known to be active at conventional doses in breast cancer. While profound myelosuppression and some mucositis was considered acceptable, agents with organ toxicity such as doxorubicin or carmustine were avoided in the construction of this transplant regimen. The use of continuous infusions of the three drugs may decrease

peak drug levels associated with toxicity. The duration of PRs was short, but CRs (whether achieved after induction or after intensification) appear to be relatively durable.

For reasons that are not immediately clear, younger women with metastatic disease in these studies had a significantly shorter disease-free and overall survival than women 40 years of age or older. There are too few patients to draw any conclusions regarding prognostic variables. Nevertheless, the percentage of CRs in women younger than 40 years was similar to that of older women as was the percentage who had received prior adjuvant chemotherapy. While the observation that younger women had a poorer prognosis is true in this particular database and of some interest, drawing definitive conclusions from an analysis of a database of this size (with 4-5 years of follow-up in patients with stage IV disease and a 1- to 2-year follow-up in locally advanced disease) would be hazardous.

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Ovarian Ablation as Treatment for Young Women With Breast Cancer

Nancy E. Davidson*

Ovarian ablation has been used for breast cancer treatment for nearly 100 years. Available methods of causing ovarian failure include surgical or radiotherapeutic ablation and LH-RH agonists that effect a reversible "medical oophorectomy." In addition, administration of certain types of chemotherapy to susceptible hosts may also result in permanent amenorrhea. The response rate to ovarian ablation in premenopausal women with metastatic breast cancer is about 35%. It is more effective in women over 35 years of age or with estrogen receptor-positive tumors. Oophorectomy, ovarian radiation, and luteinizing hormone-releasing hormone agonists are probably equally effective in this setting, although rigorous comparative trials have not been completed. Individual trials of ovarian ablation as adjuvant therapy show a trend toward increased relapse-free survival, but rarely show a survival advantage. However, an overview analysis of randomized trials of adjuvant ovarian ablation, which includes about 1800 women under 50 years of age, suggests that this modality reduces the annual rates of recurrence and death by about 25%, an effect similar to that seen with adjuvant chemotherapy by indirect comparison. Therefore, a number of clinical trials designed to elucidate the role of ovarian ablation alone or in conjunction with other adjuvant approaches are in progress. The routine use of ovarian ablation as an adjuvant therapy should await the establishment of its efficacy in these trials. [Monogr Natl Cancer Inst 16:95-99, 1994]

Ovarian ablation is the oldest form of systemic treatment of breast cancer. The efficacy of surgical oophorectomy as palliative therapy for two premenopausal women with inoperable breast cancer was reported in 1896 by Beatson (1). Yet despite the passage of nearly 100 years, surprisingly little is known about the optimal role for ovarian ablation, particularly in the management of early breast cancer. This monograph will review several aspects of this controversy, including methods available to effect an ovarian ablation, the efficacy of such approaches in the treatment of metastatic breast cancer, evidence supporting the use of such therapies in early-stage breast cancer, and ongoing clinical efforts to refine our knowledge about its use. The rationale for the use of temporary ovarian ablation as a means of breast cancer prevention as well as preliminary findings from a pilot trial are reviewed by Spicer and Pike (2).

Methods of Ovarian Ablation

Several methods of ovarian ablation are available and include oophorectomy, radiation ablation, LH-RH analogue, and adjuvant chemotherapy. However, until recently, ovarian ablation was achieved by either surgery or radiotherapy. Surgical oophorectomy has the advantage of causing an immediate and permanent reduction in ovarian hormone production. However, it does require surgery, and older series examining its use for treatment of metastatic breast cancer documented an operative mortality of up to 4.5%, depending on the general health of the patients undergoing surgery (3,4). The advent of the laparoscopic oophorectomy in recent years has greatly decreased the morbidity and mortality associated with this procedure and led to renewed interest in its use in breast cancer.

Many early studies of ovarian ablation investigated the use of radiation-induced ablation because of its ease and safety of administration in an outpatient setting. Schedules commonly employed in these studies ranged from 450 cGy in one fraction to 1000-2000 cGy given over 5-6 days (5-7). Potential disadvantages include the slower attainment of castrate hormone levels and the possibility that the ovarian ablation could be incomplete. At present, ovarian radiation is not routinely used in the United States for management of breast cancer. However, incidental ovarian radiation, which may result in a postmenopausal state, is a common consequence of radiotherapy given to palliate painful metastases in the lumbar spine or pelvis in premenopausal women.

Analogues of gonadotropin-releasing hormone (GnRH), particularly luteinizing hormone-releasing hormone (LH-RH) agonists, are a third means of ovarian ablation (8). These synthetic analogues of LH-RH differ from the naturally occurring LH-RH decapeptide by substitution of D-amino acids for L-glycine at position 6 and ethylamide or azaglycine amide for glycine amide at position 10. These modifications result in decreased degradation and increased affinity for GnRH receptor, thus increasing the molecular potency of the compounds 50- to 200-fold over native LH-RH.

GnRH is normally released in a pulsatile fashion and causes pulsatile release of LH. However, exogenous administration of continuous or intermittent high doses of GnRH analogues inhibits LH and follicle-stimulating hormone (FSH) release. This may result from longer duration of binding of the analogs to the

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GnRH receptor because of decreased degradation that in turn leads to down-regulation of receptors and internalization and degradation of occupied receptors with subsequent desensitization. Thus, although the synthetic analogues acutely raise plasma levels of estradiol and gonadotropins, their long-term administration paradoxically suppresses ovarian function, and plasma estradiol levels fall to castrate levels. A fall in plasma gonadotropins is concomitantly noted. These changes are in contrast with those observed with long-term tamoxifen use in premenopausal women. Premenopausal women receiving tamoxifen may have cyclic LH and FSH secretion and increased serum estradiol, a finding of unclear significance (9).

The primary effect of the LH-RH agonists is thus felt to be through their ability to effect a "chemical castration" that has the advantage of being reversible and nonsurgical. However, in vitro studies have documented the presence of GnRH binding sites on several human breast cancer cell lines (10), and growth inhibitory effects of these agents on cell lines have been reported (11). In addition, responses to LH-RH agonists in women with postmenopausal or steroid receptor-negative breast cancer have been reported sporadically (12-14). These findings raise the possibility that these analogues have a direct effect on the breast cancer cell as well. Of the many LH-RH agonists, synthesized, buserelin, leuprolide (Lupron), and goserelin (Zoladex) have been studied most extensively in breast cancer. Both leuprolide and goserelin are commercially available in the United States, although neither has been approved by the Food and Drug Administration for the treatment of breast cancer.

Finally, the administration of cytotoxic chemotherapy may often result in ovarian ablation. The frequency of permanent amenorrhea depends on a number of factors, including the class of chemotherapeutic agents chosen, the age of the patient, and the total dose of the agents used. Among the cytotoxic drugs, alkylating agents, like cyclophosphamide or melphalan, are the most frequent cause of ovarian dysfunction. The effects of doxorubicin are uncertain and it is unlikely that antimetabolites, including methotrexate or fluorouracil, have any significant effect (15). Older premenopausal women are more susceptible to the ablative effects of cytotoxic chemotherapy than younger women. For example, the Milan group (16) has shown that administration of the classic regimen of cyclophosphamide, methotrexate, and fluorouracil for 6 months resulted in amenorrhea in 14% of women under 36 years, 46% of those 36-40 years, and 93% of those over the age of 40 years. Finally, the likelihood of chemotherapy-induced ovarian failure is also related to the total dose of the toxic agent. In a study of young women receiving adjuvant therapy for over 1 year (17), permanent amenorrhea occurred after a mean total dose of 5.2 g of cyclophosphamide in women 40 years and older as compared with 9.3 g of cyclophosphamide in women under 40 years of age. The hypothesis that adjuvant chemotherapy exerts a portion or all of effects in premenopausal women via its ability to cause a chemical castration has been advanced. This remains an area of great controversy at the present time; however, several clinical trials directly addressing this possibility are in progress.

Ovarian Ablation for Metastatic Breast Cancer

The use of ovarian ablation results in an overall response rate of about 35% in premenopausal women with metastatic breast cancer (3-5,18-20). The likelihood of response to ovarian ablation is higher for women with steroid receptor-positive tumors, and this therapy is most effective in women who are actively menstruating, particularly those over the age of 35 years. The response rate for women under age 35 is often lower, ranging from 15% to 25% (3,21), probably because of a higher incidence of receptor-negative tumors in this group.

As noted above, ovarian ablation can be achieved by surgery, radiotherapy, or administration of LH-RH agonist. There are no completed randomized trials that directly compare these modalities as treatment for women with metastatic breast cancer. Several retrospective comparisons of surgical and radiotherapeutic ovarian ablation have been performed with variable results (3,5). However, these reports are flawed by dissimilarities between patients in the various treatment groups. In particular, in these studies, patients who were considered poor operative risks received radiotherapy rather than surgery, raising the possibility that irradiated patients had an inherently worse prognosis than those who received surgery. In summation, however, surgical oophorectomy and ovarian radiation appear to be equally effective as palliative treatment for premenopausal women with metastatic breast cancer.

Several phase II studies of LH-RH agonists for management of metastatic breast cancer in premenopausal women have also been reported (18). Response rates of 32%-50% are seen, results similar to those seen with surgery or radiotherapy by indirect comparison. A randomized trial comparing oophorectomy with long-term goserelin as first treatment for premenopausal women with steroid hormone receptor-positive metastatic breast cancer is in progress in the United States. Accrual has been slow because of the trial design, but over half of the 200 patients needed have been enrolled. When completed, this trial should provide definitive information about the comparability of these two methods of ovarian ablation.

Finally, with the growing use of tamoxifen as first endocrine therapy for premenopausal women with potentially hormone-responsive metastatic disease, the relative efficacy of tamoxifen and ovarian ablative treatments in this setting is of interest. A number of small phase II trials of tamoxifen suggest that response rate and duration are equivalent to those achieved with ovarian ablation (18). Two small randomized trials comparing tamoxifen and oophorectomy for premenopausal women with stage IV breast cancer have been published (22,23). Both trials lack statistical power because of poor accrual, but overall there was no significant difference in response rate, time to treatment failure, duration of response, or survival of patients treated with either modality. Thus, tamoxifen administration or ovarian ablation is acceptable treatment in this setting, and choice of therapy will be dictated by relative toxicity and patient preference.

Ovarian Ablation for Early Breast Cancer

Individual trials

About a dozen trials of ovarian ablation as adjuvant therapy for management of early-stage breast cancer have been per-

formed. Their interpretation is hampered by a number of difficulties. First, many of these trials are small by modern standards and frequently include both node-positive and -negative patients, diluting the statistical power of the trials to detect any differences. Few used steroid receptor status as a selection criteria, as most of these trials predated the availability of receptor analysis. Also, the trials were not always limited to premenopausal women and definitions of premenopausal versus postmenopausal varied considerably between individual trials. The treatment in these trials is heterogeneous, since ovarian ablation by radiotherapy or surgery was used, sometimes in the presence of concurrent hormonal (e.g., prednisone) or cytotoxic therapy. Finally, a minority of the studies does not formally meet the criteria for a randomized trial. For example, the Christie Hospital trial assigned patients to ovarian radiotherapy or observation by birth date rather than by standard randomization procedures, where neither physician nor patient has any a priori knowledge of what therapy the patient will receive (6,7). Nonetheless, several of these studies show a trend toward increased relapse-free survival. However, this is rarely associated with a survival advantage. A summary of some of the major published trials is presented in Table 1.

Overview analysis of ovarian ablation trials

In 1992, the Early Breast Cancer Trialists' Collaborative Group published an overview analysis of 133 randomized trials of adjuvant hormonal, cytotoxic, or immune therapy, involving 75 000 women with early-stage breast cancer (24). Twelve trials of ovarian ablation begun before 1985 were identified for inclusion in this analysis. Two large trials, the Christie (6,7) and Malmo (25) trials mentioned above, were not included since they were not considered true randomized trials. Of the 12 trials identified, two studies, the NSABP B-02-03 (26) and Boston (27) trials, were excluded from analysis as recent follow-up information could not be obtained. Thus, 10 trials were analyzed. Five were trials of ovarian ablation without concurrent cytotoxic therapy; four were studies of ovarian ablation in the presence of cytotoxic therapy; and one included patients with and without concurrent chemotherapy. The analysis used age as a surrogate for menopausal status and included 1746 women under 50 who were presumed to be predominately premenopausal.

By 15 years of follow-up, the overall difference in recurrence-free survival was $10.2\% \pm 2.7\%$ (SD), favoring the ovarian ablation group (Table 2). This recurrence-free survival benefit translated into a survival benefit of $10.6\% \pm 2.7\%$ (SD) at 15 years. These significant differences in recurrence-free and overall survival were seen in both node-negative and -positive women, although the level of significance was higher for the node-positive women. In summation, ovarian ablation across all trials was associated with a $26\% \pm 6\%$ reduction in the annual odds of recurrence and a $25\% \pm 7\%$ reduction in the annual odds of death.

Separating the women into those who did or did not receive concurrent chemotherapy suggests that the effect of ovarian ablation was somewhat smaller in the presence of chemotherapy than in its absence, presumably because some women are rendered amenorrheic by chemotherapy (Table 3). Ovarian ablation alone resulted in an approximate 30% reduction in annual

Table 1. Some major published trials of adjuvant ovarian ablation compared with no treatment control*

			<i>P</i>	
Study	Ref. No.	No. of patients	RFS	OAS
Ovarian radiotherapy				
Christie	(6,7)	598	<0.05	NS
Oslo	(30,31)	346	0.05	NS
Toronto IA	(32,33)	130	0.13	0.19
Toronto IB	(32,33)	649	0.04	0.02
Oophorectomy				
Malmo	(25)	280	NS	NS
NSABP B02-03	(26)	438	NS	NS
Boston	(27)	179	NS	NS
Saskatchewan	(34)	355	0.02	0.02
Oophorectomy with concurrent cytotoxic therapy				
Ludwig II (CMFP)	(35)	327	NS	NS
Swog 7827B (CMFVP)	(36)	288	NS	NS

*C = cyclophosphamide; M = methotrexate; F = fluorouracil; V = vincristine; P = prednisone; NS = not significant; RFS = recurrence-free survival; OAS = overall survival.

Table 2. Overview analysis of ovarian ablation for women under age 50*†

Patients	15 y RFS, %	15 y OAS, %
All		
Ovarian ablation	58.5	52.9
Control	48.3	42.3
	P = .0004	P = .00007
Node-negative		
Ovarian ablation	78.3	79.7
Control	68.9	72.9
	P = .01	P = 0.02
Node-positive		
Ovarian ablation	42.3	49.6
Control	31.9	36.5
	P = .00003	P = .0002

*RFS = recurrence-free survival; OAS = overall survival.

†Adapted from Lancet 339:1-15, 71-85, 1992.

Table 3. Indirect estimation of the effects of polychemotherapy, ovarian ablation, and tamoxifen in women under 50 with early-stage breast cancer*†

Types of systemic therapy being compared	No. of Patients	Typical reduction % (SD) in annual odds of	
		Recurrence or prior death	Death from any cause
Effect of adding ovarian ablation			
Ablation versus control	878	30 (9)	28 (9)
CTX + ablation versus CTX	939	21 (9)	19 (11)
Effect of adding CTX			
CTX versus control	2976	37 (5)	27 (6)
CTX + TAM versus TAM	386	32 (16)	-6 (23)
Effect of adding TAM			
TAM versus control	2216	27 (7)	17 (10)
CTX + TAM versus CTX	6362	7 (4)	3 (5)
Indirect estimated effects of ovarian ablation + CTX versus control	—	40%-50%?	30%-40%?

*CTX = prolonged polychemotherapy; TAM = tamoxifen.

†Adapted from Lancet 339:1-15, 71-85, 1992.

Late Effects of Adjuvant Therapy for Breast Cancer

Charles L. Shapiro, Abram Recht*

Adjuvant therapy and breast radiotherapy are routinely administered to breast cancer patients. Randomized, controlled trials provide reliable estimates of the treatment benefits and acute toxicity, but far less is known about the adverse effects of treatment that may manifest years or decades after therapy. This review will summarize what is known about the late effects of adjuvant therapy and breast radiotherapy. Most of the studies are concerned with treatment-related second cancers. Other potential adverse health effects of treatment on the cardiovascular and skeletal systems will be discussed.

Long-term Prognoses in Women With Breast Cancer

In all subsets of breast cancer patients defined by axillary nodal status, tumor size, or other clinicopathologic features, there are long-term survivors. The highest percentage of long-term survivors is found among patients without histologic evidence of metastases to ipsilateral axillary lymph nodes and among those with small invasive breast tumors. The 20-year recurrence-free survival of node-negative patients with invasive primary tumors less than 1.0 cm, 1.1-2.0 cm, and 2.0-5.0 cm is 86%, 69%, and 63%, respectively, and it is estimated that perhaps 89% (95% confidence interval [CI] = 80%-98%), 77% (95% CI = 70%-85%), and 63% (95% CI = 55%-72%) of patients in each of these groups may be cured after surgery alone (1,2). Among some subsets of node-positive patients, survival may be prolonged. The 20-year recurrence-free survival of patients with invasive primary tumors less than 2.0 cm and one to three nodal metastases is 57% (1). Even in patients with 10 or more positive lymph nodes, the 10-year recurrence-free survival rate ranges between 15% and 31% (2).

Estimating the Benefits of Adjuvant Therapy

A review of treatment-related events must also include estimates of the treatment benefits. Ultimately, these estimates are used to formulate risk-benefit analyses. A comprehensive overview or meta-analysis of all available randomized adjuvant trials was performed by the Early Breast Cancer Trialists' Collaborative Group; the 10-year results are presented in Table 1 (3). Most women were node positive, but 25% in the chemotherapy trials and 43% in the tamoxifen trials were node negative. Adjuvant chemotherapy reduces the annual odds of death by 25% \pm 5% in women under age 50 years. In women over age 50 years, chemotherapy reduces the annual odds of death by 12% \pm 4%, and tamoxifen reduces the annual odds of deaths by 20% \pm 2%.

Proportional reductions in the odds of death describe the treatment benefits only in those who might have died during the observation period. Alternatively, the magnitude of treatment benefit for all patients is described by determining the absolute reduction in the number of deaths. For example, if 10 000 women under the age of 50 years are treated with adjuvant chemotherapy, about 1000 lives will be saved during the first 10 years after treatment (3). In the node-negative patients, the absolute reduction in breast cancer deaths will be smaller (about 200-400 lives saved per 10 000 treated women under age 50 years), since the majority of these patients have localized cancers and are not at risk of systemic metastases.

Methodologic Problems in the Analysis of Treatment-Related Late Events

Reliable estimates of treatment-related events are difficult to obtain. Until recently, most breast cancer patients treated with adjuvant therapy were node positive, a group in which early cancer mortality is relatively high. Therefore, fewer node-positive patients may survive long enough to develop treatment-related events. Conversely, patients with prolonged cancer-free survival are also at risk of the competing non-breast cancer

Table 1. Benefits of adjuvant therapy*

Adjuvant therapy	Proportional reduction in annual odds of death (%) \pm SD	Absolute reduction in 10-y mortality per 10 000 women treated
Age < 50 Chemotherapy	25 \pm 5	1000
Age \geq 50 Chemotherapy	12 \pm 4	500
Tamoxifen	20 \pm 2	800

Node-negative†
200-400
Node-positive‡
600-1200

*Modified from Early Breast Cancer Trialists' Collaborative Group. Lancet 1:1-15, 71-85, 1992.

†10-year risk of breast cancer death, 10%-20%.

‡10-year risk of breast cancer death, 40%-80%.

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causes of morbidity and mortality prevalent in the general population. The result is that fewer patients can be observed for the development of treatment-related events, and it is more difficult to accurately estimate the incidence of such events. Accurate diagnosis of a treatment-related event may also depend on when it occurs. Non-breast second cancers are more apt to be correctly identified if they occur as the first event after the initial treatment of breast cancer (4). Second cancers, which occur after a documented breast cancer relapse, may be assumed to be further metastases and their diagnostic work-up deemed of lesser importance.

Information about treatment-related events is derived from several sources. These include the randomized trial, the cohort study, the case-control study, and the case report (5). The randomized prospective trial is the best source to determine whether the treatment caused an adverse event. However, most randomized trials do not have a sufficiently large sample size to detect an increase in the frequency of a rare event, such as acute nonlymphocytic leukemia (ANLL), with adequate statistical power (6). Retrospective case-control and cohort studies are the primary sources for treatment-related events. These studies are generally performed using tumor registries and are subject to many potential sources of bias (5,7). Data from tumor registries may be incomplete or what is reported to the registry may underestimate or overestimate the association between a particular treatment and an adverse event. In the Surveillance, Epidemiology, and End Results Program (SEER) registry, there were higher rates of retrospective reporting of chemotherapy in breast cancer patients who developed leukemia as compared to patients who did not develop a subsequent cancer (8).

It is axiomatic that estimates of treatment-related events are based on clinical trials that were designed decades ago. In some cases, a particular drug is no longer in vogue, or the patient population substantially differs from that treated in earlier studies. The seminal studies of the National Surgical Adjuvant Breast and Bowel Project (NSABP) illustrate these points. Beginning in 1971, the NSABP initiated a series of randomized, controlled adjuvant trials of melphalan (L-PAM) for 2 years in over 8000 node-positive breast cancer patients. In 1985, a 10-year analysis of treatment-related leukemia's was presented (9). Despite the importance of this study, it is of little relevance to current treatment practices. Nowadays, adjuvant chemotherapy regimens no longer contain L-PAM, the typical duration of

treatment is substantially shorter than 2 years, and node-negative patients are the group for whom treatment-related events are of most concern.

Secondary Leukemia After Adjuvant Chemotherapy

Alkylating agents, given singly or in combination with other drugs, have been components of virtually all adjuvant regimens during the past 30 years. Alkylating agents damage deoxyribonucleic acid, resulting in cell death or sublethal genetic damage (10). Sublethal mutations or chromosomal loss in normal hematopoietic precursor cells is thought to be the mechanism for the leukemogenic properties of these drugs (11-13). Among the various leukemias, ANLL and myelodysplastic syndromes are related to alkylating agent exposure.

The risk of ANLL is primarily affected by the specific alkylating agent and the total cumulative dose or duration of drug exposure. The relative risk of ANLL after adjuvant chemotherapy is described in Tables 2 and 3. Breast cancer patients treated with surgery alone and not exposed to chemotherapy do not appear to have higher than expected rates of ANLL compared with the normal population. The relative risk of ANLL after adjuvant chemotherapy ranges between 1.3 and 24. It may be more meaningful to convert relative risk to an estimate of the number of excess cases of ANLL per 10 000 treated women using the following formula: $(\text{relative risk} - 1) \times (\text{the expected incidence of ANLL per 10 000 women-years at risk}) \times (\text{the number of years at risk})$ (14). After adjuvant chemotherapy, between 1.5 and 109 excess cases of ANLL per 10 000 treated women would be expected during a 10-year period.

It is important to consider that adjuvant regimens no longer contain L-PAM, the alkylating agent responsible for the vast majority of treatment-related ANLL in breast cancer patients. L-PAM and cyclophosphamide differ in their leukemogenic potential (8,13-15). The relative risk of ANLL after L-PAM is between 24 and 44, but the risk after cyclophosphamide is only between 1.3 and 3 (Table 3). The latter corresponds to between one and 10 excess cases of ANLL per 10 000 women treated with cyclophosphamide. Higher cumulative drug doses, which until recently reflected longer treatment durations, also increase the relative risk of ANLL. In early adjuvant trials, the treatment duration was often 1 or 2 years. Shorter durations of adjuvant

Table 2. Relative risk of ANLL after adjuvant chemotherapy

Study	Type	Years	Relative risk			Absolute 10-y excess mortality per 10 000 women treated with chemotherapy	Ref. No.
			Surgery only	Radiation	Chemotherapy		
Curtis (1984)	Cohort	1973-1980	1.4	3.7*	8.1*	34	(141)
Harvey (1985)	Cohort	1935-1985	1.2	2.5†	—	—	(103)
Fisher (1985)	Randomized	1971-1981	2.6	10.3*	24.0*	109	(9)
Haas (1987)	Case-control	1960-1980	—	0.86	1.3	1.5	(15)
Curtis (1989)	Case-control	1935-1982	—	1.22	—	—	(17)
Curtis (1990)	Case-control	1973-1985	1.4	—	11.5*	50	(8)
Curtis (1992)	Case-control	1973-1985	1.0	2.4†	10.0*	43	(14)

* $P < .01$.

† $P < .05$.

Table 3. Relative risk of ANLL by alkylating agent

Drug	Study	Relative risk	Absolute 10-y excess mortality per 10 000 treated women	Ref. No.
L-PAM	Fisher (1985)	24.0	109	(9)
	Curtis (1990)	44.6	208	(8)
	Curtis (1992)	31.4	148	(14)
Cyclophosphamide	Haas (1987)	1.3	1	(15)
	Curtis (1990)	1.3	1	(8)
	Curtis (1992)	3.1	10	(14)

chemotherapy, on the order of 6 months, have been shown to be of comparable therapeutic efficacy to longer durations (3). The absolute risk of ANLL associated with a typical 6-month course of standard-dose adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) is about five excess cases per 10 000 treated women at 10 years (14).

How does the risk of ANLL compare to the benefits of a typical 6-month course of adjuvant CMF? Adjuvant chemotherapy might be expected to save about 1000 lives per 10 000 treated women under the age of 50 (Table 1). Treatment-related ANLL is invariably fatal, so the excess cases could be considered treatment-related deaths. A risk-benefit analysis limited to ANLL (1000 lives saved versus about five excess leukemic deaths) clearly favors the use of adjuvant chemotherapy because the risks of ANLL are too small, even in the most favorable subsets of node-negative breast cancer patients.

Secondary Leukemia After Postmastectomy Irradiation

Exposure to ionizing radiation is also linked to the development of ANLL (16). The leukemogenic effects of radiotherapy must be interpreted with respect to the volume of bone marrow irradiated and the total dose (14,17). These effects depend on the treatment techniques and the field arrangements, both of which have markedly changed during the past 40 years. Virtually all studies of ANLL after radiotherapy for breast cancer are of postmastectomy chest wall and nodal irradiation. The relative risks of ANLL are estimated in Table 2. No increase, or perhaps a slight increase in the relative risk of ANLL, on the order of 2-4, is observed in most of these studies. It has been suggested that the risk of ANLL may be overestimated in registry studies due to the unreported use of radiotherapy in the controls and the unreported use of chemotherapy in the cases (17). Higher doses of radiation to the total active bone marrow in excess of 9 Gy were associated with statistically significant higher relative risks of ANLL, independent of the effects of alkylating agents (14). However, radiation doses of less than 9 Gy to the total active bone marrow were not associated with statistically significant increases in the risk of ANLL.

In contrast to other studies, a 10-fold increase in ANLL was observed in 1116 patients treated with radiation alone after surgery in two NSABP trials (9). However, this higher relative risk was based on only four cases of ANLL compared with the expected incidence of 0.39 in an age-matched population. Given so few cases, the lower limit of the 95% CI surrounding the 10-

fold increased relative risk reported in the NSABP trials overlaps with the twofold to fourfold increase in the relative risks of ANLL observed in other studies (17).

The NSABP trials afford the opportunity to contrast the effects of postmastectomy chest wall and nodal irradiation with breast radiotherapy after lumpectomy. All four cases of ANLL occurred in 646 patients treated with postmastectomy irradiation (trial B-04), whereas none were observed in the 470 patients treated with breast radiotherapy (trial B-06). This observation is consistent with a lower dose of radiation to a smaller volume of bone marrow after breast radiotherapy as compared with postmastectomy chest wall and nodal irradiation.

The risk of ANLL after breast radiotherapy is likely to be nil or perhaps too small to detect, judging from the low risks of ANLL after postmastectomy irradiation. A potentially more important question is whether the risk of ANLL is higher after combination therapy for adjuvant chemotherapy and radiotherapy. This question has not been evaluated in most breast cancer studies. The risk of ANLL does not appear to be increased in ovarian cancer and Hodgkin's disease after both treatments, compared with chemotherapy alone (13,18-20). In contrast, the relative risk of ANLL was higher in breast cancer patients who received alkylating agents and postmastectomy irradiation (relative risk = 17.4; 95% CI = 6.4-47) than in patients who received alkylating agents alone (relative risk = 10; 95% CI = 3.9-25.2) or radiation alone (relative risk = 2.4; 95% CI = 1.0-5.8) (14). However, the differential effects of L-PAM and cyclophosphamide on the risks of ANLL were not considered in this analysis. Further information should be available in the future from the Danish Breast Cancer Cooperative Group Trial 82-b, which randomized 2028 premenopausal patients to CMF alone, CMF plus tamoxifen, or CMF plus postoperative radiotherapy (21,22).

The risk of ANLL after standard-dose adjuvant cyclophosphamide or postmastectomy chest wall irradiation is exceedingly small and of little clinical relevance. Whether these modalities interact to increase the risk of ANLL is less certain but of potential importance now that standard treatment practices include breast radiotherapy and adjuvant chemotherapy. It is likely, however, that the risks of ANLL after combined modality treatment will be very small. Perhaps the most important question is whether the higher total doses of alkylating agents being administered in current high-dose adjuvant trials will result in a higher risk of ANLL.

Cardiac Effects of Adjuvant Chemotherapy

Doxorubicin directly damages myocardial cells in a cumulative dose-dependent manner and manifests as cardiomyopathy and congestive heart failure (23,24). Doxorubicin-related congestive heart failure usually occurs within weeks to months after treatment and is often fatal. The risk of doxorubicin-related congestive heart failure is most strongly related to the cumulative dose, particularly when the total is in excess of 550 mg/m² (23,24). Other risk factors for cardiac toxicity include the schedule of administration with higher risks after bolus infusions versus lower risks after continuous infusions or low-dose weekly infusions, older age, prior history of underlying cardiac disease, and possibly mediastinal irradiation (23). Limit-

ing the total doxorubicin dose to between 200 and 300 mg/m², as is typical of adjuvant regimens, results in an estimated incidence of doxorubicin-related congestive heart failure of 0.1%-1% in breast cancer patients (25,26).

Few studies have evaluated the potential long-term cardiac effects of adjuvant doxorubicin in breast cancer patients. Such inquiry is stimulated by the experience of pediatric leukemia patients after treatment with doxorubicin. Subclinical echocardiographic abnormalities of left ventricular function have been observed for a median of 6-7 years after treatment in 23%-57% of pediatric leukemia patients (27,28). These patients received a median cumulative total doxorubicin dose of 360-450 mg/m². Importantly, the frequency and severity of the abnormal echocardiographic findings increased as the duration of follow-up extended beyond 10 years (27,28). Late-appearing episodes of congestive heart failure, ventricular arrhythmia, and sudden deaths also have been observed in these patients. Possibly, the pediatric heart is more susceptible to late cardiac effects because doxorubicin may impair myocardial growth below the level required for the normal adult (27). This hypothesis is supported by a small study in which pediatric patients who received doxorubicin were found to have late myocardial dysfunction, but no evidence of myocardial dysfunction was detected in the patients over age 25 years when they received doxorubicin (29).

Treatment-related cardiac effects in adults are more difficult to evaluate. The increasing prevalence of cardiac disease in the aging population compounds the problem. In a long-term follow-up study of 23 lymphoma patients treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), congestive heart failure developed in 17% of the CHOP-treated patients and in 15% of an age-matched group of colon cancer patients treated with surgery alone (30). Thus, it is difficult to determine whether doxorubicin contributes to late cardiac toxicity, given the high background incidence of cardiac disease in the population. Cardiac comorbidity is particularly relevant in breast cancer patients, since after menopause the rates of cardiovascular disease increase in women and by the sixth decade are similar to those of men (31).

Late cardiac effects after adjuvant doxorubicin have been evaluated in two large retrospective series (26,32). After a median follow-up of more than 5 years, investigators at the M. D. Anderson Cancer Center observed a 1% incidence of doxorubicin-related congestive heart failure in 400 stage II and III patients treated with 300 mg/m² doxorubicin and a 4% incidence in 134 stage IV patients treated with 450 mg/m² (26). The median time from the last dose of doxorubicin until the onset of congestive heart failure was 1 month, and no cases developed more than 33 months after completing the therapy. A subset of these patients has been followed for more than 10 years, and no additional doxorubicin-related cardiac events have developed (33). In 7% of the study, cardiac disease was attributable to causes other than doxorubicin, including hypertension or coronary artery disease. However, it is uncertain whether the doxorubicin might directly contribute or act as a risk factor for subsequent cardiac disease.

More recently, the incidence of congestive heart failure after adjuvant CMF alone or CMF plus 300 mg/m² doxorubicin was evaluated in over 800 patients who participated in three ad-

juvant trials (34). The doxorubicin dose was 75 mg/m² every 3 weeks by bolus infusion. Forty-four percent of patients also received breast radiotherapy concurrent with chemotherapy. After a median follow-up of nearly 7 years, the incidence of congestive heart failure was 0% in CMF-treated patients and 0.8% in those who received CMF plus doxorubicin. The risks of congestive heart failure were higher in patients who also received left-sided breast radiotherapy (2.6%) (*see below*).

The vast majority of the doxorubicin-treated study patients experienced no adverse cardiac events. Though these data are reassuring, the median follow-up (about 7 years) was relatively short, so possibly more cardiac events will occur with longer follow-up. The study population also varied with respect to nodal status. More doxorubicin-treated patients had four or more positive nodes, so fewer of them will survive to be observed for late cardiac events. Finally, sensitive tests of myocardial dysfunction were not performed in this or in the M. D. Anderson study. These factors may underestimate the true incidence of late treatment-related cardiac events (35). Additional studies, particularly from randomized, prospective adjuvant trials, are required to fully appreciate the cardiac effects of adjuvant doxorubicin.

Cardiac Effects of Radiation Therapy

Radiotherapy may cause either acute or chronic damage to the heart (36). However, it is difficult to estimate the magnitude of this risk, as most published studies on this subject have been in patients treated with outmoded radiotherapy techniques and, hence, are of little relevance today. In a meta-analysis of randomized trials of postmastectomy irradiation, the overall mortality was similar between irradiated and control patients during the first 10 years (37). It was only during the second decade that a detectable increase in mortality was observed in patients randomized to receive irradiation. The higher mortality was the result of an increased number of cardiovascular deaths, particularly among patients with left-sided breast cancers (38,39). These trials used outmoded treatment techniques, including lower energy sources (e.g., orthovoltage units), overlapping field arrangements, and larger fraction sizes that result in substantially higher radiation doses to larger volumes of the heart than those given with modern radiotherapy techniques (36,40).

The risk of radiotherapy-related cardiac mortality was evaluated in a recent trial of 960 patients randomized to receive preoperative radiotherapy, postoperative radiotherapy, or modified radical mastectomy alone (41). The preoperative group was treated with tangential cobalt-60 fields to the breast and chest wall, while nearly all patients in the postoperative group were treated with electrons. All patients received supraclavicular and axillary irradiation. Originally, treatment included both internal mammary node chains, but after 1973 only the ipsilateral internal mammary nodes were included. The total dose of 4500 cGy was given in 180 cGy daily fractions over 5 weeks. In a small number of patients, computerized tomography (CT) scans were used to retrospectively estimate the proportion of the heart treated and the dose given with these varying techniques. The median follow-up in surviving patients was 16 years (range, 13-19 years).

Although there was an improvement in overall survival in the irradiated groups, compared with the control group, the risk of death due to ischemic heart disease was increased in patients who received large doses of radiation to substantial volumes of the heart. In patients treated with surgery alone and no radiation, the risk was 2.3 deaths per 1000 women-years at risk (WYR). Patients in the "low-dose-volume" group (i.e., those treated with right-sided cobalt-60 tangential fields that included one or both internal mammary chains) and patients in the "intermediate-dose-volume" group (i.e., those treated with electron fields to the heart) had risks of 1.5 and 2.2 deaths per 1000 WYR, respectively. However, in the "high-dose-volume" group (i.e., patients treated with left-sided tangential fields, including either one or both internal mammary chains), the risk was statistically significantly elevated at 7.1 deaths per 1000 WYR. These data clearly demonstrate the importance of reducing the radiation dose and volume of heart irradiated.

The increased risk of cardiac mortality noted in the studies discussed above could have been due (at least in part) to damage to the coronary arteries as well as the myocardium. Among irradiated patients with left-sided tumors, the left anterior descending, left circumflex, and right coronary arteries were also exposed to large radiation doses when orthovoltage techniques were employed in the past (40). In a recent study conducted at the Joint Center for Radiation Therapy (JCRT) using current treatment techniques, spiral CT scans were performed on patients with left-sided breast cancers placed in the treatment position (42). Using carefully timed contrast administration, the course of the coronary arteries could be seen directly. Only the left anterior descending coronary artery and, occasionally, part of the left main coronary artery were commonly included in the treatment fields. However, the length of the treated artery was quite variable from patient to patient and further studies of this issue are needed (JCRT: unpublished data).

Modern radiotherapy techniques expose smaller volumes of the heart to substantially lower doses of radiation than in previous experience, so it is unlikely that cardiac mortality be substantially increased over the expected background incidence. The internal mammary nodes are rarely irradiated deliberately in patients with early-stage breast cancer, so the volume of the heart treated is even smaller than in the "low volume" subgroup in the Stockholm study (43-45). The average volume of the heart included in tangential breast fields as determined by CT is 12% in left-sided cancers and none in right-sided cancers (46). The addition of a hockey-stick field to the tangents increases the volume of heart treated to 40%-60% in left-sided cancers and 17%-24% in right-sided cancers. However, the routine use of the hockey-stick field to treat the internal mammary and supraclavicular lymph nodes is no longer recommended (47). Further follow-up of the large, randomized trials comparing breast-conservation therapy to mastectomy should lead to more definitive conclusions about the effects of modern treatment techniques on the risk of late cardiac mortality.

Interactions of Radiotherapy and Chemotherapy

Radiation and doxorubicin in combination may increase the risk of cardiac toxicity (24,48,49). Symptomatic congestive

heart failure has been observed in four patients with left-sided lesions who received breast radiotherapy and concurrent doxorubicin (50). No cardiac toxicity was seen among patients treated to the right breast. In a subsequent report, electrocardiographic changes were more frequent in patients treated to the left breast when doxorubicin was given (16%), compared with CMF alone (3%), but the risk of symptomatic heart disease (pericarditis, arrhythmias, and ischemia) was no different between these two groups (32). Increased patient age (>55 years) and a previous history of heart disease also seemed to increase the risk of cardiac disease.

However, an increased risk of cardiac disease in patients receiving doxorubicin and radiotherapy has not been observed in all studies. The incidence of cardiotoxicity was similar in stage III mastectomy patients randomized to receive radiotherapy following doxorubicin-containing chemotherapy (4%) or chemotherapy alone (5%) (51). In two other trials, no episodes of cardiomyopathy were seen among patients treated with a doxorubicin-containing regimen and irradiation that included the use of direct parasternal fields (52,53).

The studies cited above vary with respect to patient selection (age, menopausal status), treatment (total doxorubicin dose, concurrent versus sequential radiotherapy), and duration of follow-up. These factors are all likely to impact on cardiac toxicity and limits drawing definitive conclusions about whether combined modality treatment enhances the risk. It seems prudent to suggest that large doses of doxorubicin should not be given concurrently with irradiation of the left breast or chest wall. Much longer follow-up will be needed to fully assess the risks of cardiac toxicity in combined-modality programs.

Contralateral Breast Cancer After Breast Radiation

Contralateral breast cancer is the most frequent second cancer in breast cancer patients. The annual risk of contralateral breast cancer is 0.3%-1.0% per year and is constant for at least 15-20 years (54,55). Factors that affect the underlying risk of contralateral breast cancer are the histology, age, and family history. The risk of contralateral breast cancer is two to four times higher in patients with invasive and in situ lobular cancers (55,56). Synchronous lobular cancers diagnosed after mirror image biopsy of the contralateral breast contribute, in part, to the increased risks. Patients under the age of 45 years at the time of diagnosis are approximately at twofold higher risks of contralateral breast cancer (55,57,58). Possibly, genetic factors contribute to the higher risks of contralateral breast cancer observed in younger women.

Does radiation for breast cancer increase the risk of contralateral breast cancer? Two observations support the biologic plausibility of this hypothesis. Radiation exposes the contralateral breast to low-dose ionizing radiation, and low-dose ionizing radiation is a breast cancer carcinogen. Postmastectomy irradiation and breast radiotherapy expose the contralateral breast to an average total dose of between 2 and 7 Gy (14,59,60). Women exposed to low-dose radiation under such diverse circumstances as the Nagasaki and Hiroshima bombings, multiple fluoroscopic examinations, irradiation for post-

partum mastitis, and mantle irradiation for Hodgkin's disease have elevated risks of subsequent breast cancer (61-64). The minimum latency period between the radiation exposure and detectable increases in breast cancer risk is about 10 years. Radiation exposure in younger women, particularly those exposed in their teenage years and 20s, results in the highest risks of subsequent breast cancer. The risks then decrease with advancing age of exposure and are not detectable in women after age 40.

In most studies, there is no detectable increase in the overall risk of contralateral breast cancer after ipsilateral postmastectomy irradiation (Table 4). The risk is slightly elevated if the analysis is restricted to contralateral breast cancers which occur 10 or more years after the radiation exposure (57,58,65). This is consistent with the previously described latency period. An analysis by the age of radiation exposure suggests that younger women may be at slightly higher risks of contralateral breast cancer. In contrast to women over the age of 45 years, the relative risk of contralateral breast cancer was significantly elevated (1.59 [95% CI = 1.07-2.36]) in women less than age 45 years who received breast radiation (65). In this study, the possible confounding effects of lobular histology and family history were not specifically evaluated. Age at radiation exposure does not increase the risk of subsequent contralateral breast cancer in other studies (56,66).

Most randomized trials of mastectomy versus breast radiotherapy do not provide details about contralateral breast cancer rates (67-70). In several recent trials, patients with either intraductal or invasive cancers were randomized to surgery with or without breast radiotherapy (71-73). No increase in the incidence of contralateral breast cancers among irradiated patients has been observed. However, the follow-up in these trials is limited to less than 4 years, and women less than age 45 represent a minority of the patients. The minimum latency period for radiation-associated breast cancer is about 10 years, so it is too early to conclude that radiation does not impact on the contralateral breast cancer risk. In addition, a small increase in contralateral breast cancer risk in women younger than age 45 years may not be detectable due to limited statistical power.

Whether radiation increases the risk of subsequent contralateral breast cancer in younger women is uncertain. If the risks are slightly elevated, how many excess contralateral breast cancers might be expected in women irradiated under the age of 45 years? There are about 63 excess contralateral breast cancers per 10 000 treated women per 1 Gy of exposure at 10 years

(65,74). The expected number of contralateral breast cancers unrelated to radiation would be about 900-1000 per 10 000 women at 10 years.

Additional studies in younger women are required to determine whether breast radiation increases the risk of contralateral breast cancers. The increasing prevalence of ductal carcinoma in situ and the recent studies supporting the use of breast radiotherapy to treat these lesions further emphasize the importance of this question (72). Avoidance of a wedge in the medial tangent field may further reduce the radiation dose to the contralateral breast (59). Treatment factors other than radiation may affect the rate of contralateral breast cancers. Adjuvant tamoxifen, and possibly chemotherapy, decrease the risk of contralateral breast cancers (56,75). In subsequent studies, the effects of these treatments will need to be considered.

Second Cancers After Adjuvant Chemotherapy

Second non-breast cancers after exposure to adjuvant chemotherapy have been analyzed in several randomized, controlled trials and in nonrandomized trials (4,18,76-78). Thus far, no detectable increase in second non-breast cancers has been observed. After 10 years of median follow-up, the cumulative frequency of second non-breast cancers was 4.2% in patients randomized to adjuvant CMF and 4% in the untreated control group (78). However, it is important to consider that 10 years may be too short an interval to exclude an increase in the incidence of epithelial cancers.

The intriguing possibility that adjuvant chemotherapy may decrease second non-breast cancers has been suggested (4). Second non-breast cancers were analyzed in over 1100 mastectomy patients randomized to either postmastectomy irradiation or 12 months of adjuvant CMF. At 10 years, the incidence of second cancers was 1% in CMF-treated patients and 6% in the irradiated patients ($P = .0003$). The incidence of second cancers was 5% in an untreated historical control group, comparable to that observed in the patients treated with radiation. This observation requires additional confirmation.

Second Cancers After Tamoxifen

There are numerous cases of endometrial cancer occurring in breast cancer patients on tamoxifen. Tamoxifen is both an estrogen antagonist and agonist, and the endometrium and other tissues are responsive to the estrogen agonist properties of the drug (79). A small, but statistically significant, increase in endometrial cancers has been observed among tamoxifen-treated patients in two large randomized, controlled trials [Fisher et al. (80A)]. In the Stockholm trial, nearly 1900 postmenopausal mastectomy patients were randomly assigned to receive 40 mg of tamoxifen per day or no treatment (80). Patients with positive axillary nodes or tumors larger than 3 cm were further randomly assigned to receive postoperative irradiation or CMF. After a median follow-up of 4.5 years, 1.4% of the tamoxifen-treated patients and 0.2% of the controls developed endometrial cancer ($P < .01$). Importantly, the incidence of endometrial cancer increased with increasing tamoxifen treatment durations from 2 to 5 years.

Table 4. Relative risk of contralateral breast cancer after breast radiation

Study	Type	Years	Relative risk	Ref. No.
McCredie (1975)	Cohort	1953-1971	Not increased	(54)
Hankey (1983)	Cohort	1935-1959 1960-1975	1.2 1.4	(57)
Basco (1985)	Case-control	1946-1982	Not increased	(66)
Storm (1986)	Cohort	1943-1980	2.5	(58)
Horn (1988)	Case-control	1975-1983	0.9	(56)
Parker (1989)	Cohort	1955-1979	Not increased	(142)
Kurtz (1988)	Cohort	1960-1981	Not increased	(89)
Boice (1992)	Case-control	1935-1982	1.2	(65)

The NSABP trial B-14 randomly assigned more than 2800 node-negative, estrogen receptor-positive women to receive either 20 mg of tamoxifen per day or placebo for 5 years (80A). After a mean follow-up of 8 years, the average annual hazard rate for endometrial cancer was 1.6 per 1000 women on tamoxifen versus 0.2 per 1000 women receiving placebo. This corresponds to a relative risk of endometrial cancer of 7.5 (95% CI = 1.7-32.7). Possibly, this relative risk is somewhat higher because of the lower than expected rate of endometrial cancer observed in the placebo-treated patients. In other studies, the average annual hazard rate for endometrial cancer in breast cancer patients not treated with tamoxifen is about 0.7 per 1000 (80A). If this estimate is used as the background rate, tamoxifen may be associated with about a twofold increase in the risk of endometrial cancer.

The results of NSABP trial B-14 show that the 20-mg daily dose of tamoxifen is associated with a small increase in the risk of endometrial cancer. Thus far, no apparent increase in endometrial cancers has been observed in other smaller adjuvant tamoxifen trials with comparable durations of follow-up (75,80A). The small risk of endometrial cancer in NSABP trial B-14 may be weighed against the benefits of tamoxifen to reduce the rates of breast cancer relapse and contralateral breast cancer. In such an analysis, after 5 years, a total of about six endometrial cancers per 1000 treated women would be expected to occur compared with 104 fewer breast cancer relapses and three fewer contralateral breast cancers per 1000 treated women (80A). The latter corresponds to a 46% reduction in the breast cancer relapse rate and a 42% reduction in the contralateral breast cancer rate at 5 years. Most would agree that the benefits of tamoxifen far exceed the risks of endometrial cancer in women with early-stage breast cancer.

The histologic features and prognosis of 17 patients with tamoxifen-related endometrial cancers in the Stockholm trial have been reported (81). The median tamoxifen treatment duration was 24 months (range, 6-60 months), and the median time between starting tamoxifen and the diagnosis of endometrial cancer was 32 months (range 6-130 months). Virtually all of the tumors were of low histologic grade and stage, similar to the findings with endometrial cancers which are related to exogenous estrogens. The 10-year actuarial survival of patients with tamoxifen-related endometrial cancers was comparable to that in the entire Swedish population. Of the 23 tamoxifen-related endometrial cancers in NSABP trial B-14, 88% were stage I, and 78% were of favorable or intermediate histologic grade (80A). The mean time between starting tamoxifen and the diagnosis of endometrial cancers was \pm 6 months, and 36% of the endometrial cancers were diagnosed within 2 years of starting treatment. Four tamoxifen-treated patients died of endometrial cancer or the complications of treatment for endometrial cancer.

Most of the endometrial cancers diagnosed in the Stockholm and NSABP trials were stage I and of favorable histology. In contrast are the results of a small retrospective study in which the tamoxifen-related endometrial cancers were more likely to be of high grade and to be poorly differentiated compared with endometrial cancers in a non-tamoxifen-treated group of breast cancer patients (82). The tamoxifen-treated patients in this study received 40 mg/d, and the mean duration of tamoxifen treatment

was about 6 years. The disparity between the results of these studies may be explained by selection factors, treatment factors, or perhaps the small number of cases included in each series.

Possibly, the endometrial cancers diagnosed after relatively short durations of tamoxifen treatment are the result of increased surveillance (so-called detection bias) (82). Although routine endometrial sampling or endovaginal ultrasound has been suggested by some, the overall incidence of endometrial cancer in tamoxifen-treated patients may be too small to justify screening all asymptomatic patients (83). Women on tamoxifen should be advised to have annual gynecologic examinations and to seek a gynecologic evaluation should they develop postmenopausal bleeding or any other gynecologic symptoms.

In animals, the other second cancer linked to tamoxifen is hepatocellular carcinoma (84). Thus far, evidence for this is lacking in randomized, controlled adjuvant tamoxifen trials. In the Stockholm study discussed above, two tamoxifen-treated patients developed liver cancer, and no liver cancers have been observed thus far in NSABP trial B-14 (80,80A). No increase in liver cancer has been observed in a Danish trial in which patients were randomly assigned to receive 30 mg per day or to receive no treatment (85). Anecdotal cases of hepatitis, hepatic failure, or other hepatobiliary complications in tamoxifen-treated patients have been reported (84).

Tamoxifen appears to reduce the rate of contralateral breast cancers (75). However, in one randomized, controlled trial, the effect of tamoxifen on contralateral breast cancer risk varied according to menopausal status (86). Tamoxifen-treated postmenopausal patients experienced a lower risk of contralateral breast cancer, whereas for premenopausal patients, the risk was increased. This observation has yet to be confirmed in any other study.

Second Cancers After Radiation Therapy

Radiation-induced sarcomas in breast cancer patients have recently been reviewed (87,88). The mean latency period between treatment and radiation-induced sarcoma is about 10 years, but cases have been reported 24 years after treatment (89-91). Angiosarcomas appear to have a slightly shorter latency period (92-96).

The estimated incidence of sarcomas after postmastectomy orthovoltage irradiation was 0.2% (97). In a registry study in which the majority of patients were treated with orthovoltage techniques, 18.2 excess sarcomas per 100 000 patient-years of follow-up were observed (80). The risk of sarcoma appears lower in patients treated with megavoltage equipment. Using the more modern treatment techniques, the estimated incidence of sarcoma was nine to 10 per 100 000 patient-years of observation, and the 10-, 20-, and 30-year actuarial incidence of sarcoma was 0.2%, 0.43%, and 0.78%, respectively (89,91).

An exponential dose-induction relationship for bone sarcomas has been suggested (98). In particular, a very low incidence of sarcoma was associated with doses below 5000 cGy; the incidence increases above 0.1% at doses of 7000-8000 cGy. The future incidence of sarcomas may be lower than that seen in the past due to changes in the treatment techniques. In particular, nearly all patients with radiation-induced sarcomas were

irradiated to multiple fields, in order to treat the regional lymph nodes. When this is done, "hot spots" are common (i.e., regions of substantial overdose due to overlaps between treatment fields). In the JCRT experience, two of the three radiation-induced sarcomas appeared in probable field overlaps in patients treated with imperfect matching techniques (99). Most patients now receive breast radiotherapy alone. If nodal treatment is prescribed, multiple techniques are available to avoid matchline overlap entirely (44).

The incidence of radiation-related sarcomas is likely to be extremely low among patients treated with current radiotherapy techniques. Radiotherapy might also increase the risk of lung cancer. In the one randomized, postmastectomy irradiation trial with prolonged follow-up, no increase in lung cancer has been observed (39). The follow-up in other trials is too short to exclude an increased risk of lung cancer occurring more than 10 years after treatment (85,100). Two case-control studies show a modest twofold to threefold elevation in the relative risks of ipsilateral lung cancer more than 10 years after treatment (101,102). No increase in contralateral lung cancers was observed. These patients were treated predominantly with orthovoltage equipment. An estimated seven to eight excess lung cancers per 10 000 irradiated women who survived more than 10 years were observed in another study (103). It is important to consider the possible effects of cigarette smoking on the risks of radiation-induced lung cancers. Synergism between these factors has been observed in studies of survivors of the atomic bomb and uranium miners (104). In one study in which smoking history was recorded, there appeared to be a substantially increased risk of lung cancer in irradiated patients who smoked, compared with patients with neither exposure (101,102). However, in most studies the smoking history is not available.

The risk of radiation-related lung cancer is uncertain, but likely to be extremely low, using modern treatment techniques that result in smaller volumes of the lung being irradiated (46). Nonetheless, it seems prudent (for many reasons) to counsel irradiated patients to stop smoking.

Chemotherapy-Induced Premature Ovarian Failure: Implications for Treatment-Related Events

Virtually all studies of treatment-related events are concerned with second cancers. These are rare occurrences. Of greater potential significance is the possible adverse effects of chemotherapy-induced premature ovarian failure, a prevalent side effect of adjuvant chemotherapy. Cytotoxic drugs, particularly alkylating agents, cause primary ovarian failure (105-109). Breast cancer patients who develop ovarian failure experience decreases in estradiol and increases in gonadotropins similar to those observed in postmenopausal women (106,107,109). Ovarian failure occurs in as many as 63%-85% of breast cancer patients treated with CMF (110-114). Age is a major determinant of chemotherapy-induced ovarian failure. Permanent ovarian failure will occur in 30%-50% of women under the age of 40 years and in 90% or more of those over the age of 40 (110-112).

The risks of osteoporosis and cardiovascular disease may be increased in women with premature ovarian failure. Obligate

bone loss begins after the age of 35 years and is affected primarily by menopause (estrogen deficiency) and aging (115-117). The important clinical sequelae of menopausal and age-related bone loss is the development of skeletal fractures or osteoporosis. This is prevalent in the general population where one third of women over the age of 65 develop a spinal fracture and, by extreme old-age, one third of them develop a hip fracture. The development of skeletal fractures depends on a variety of genetic, endocrine, and nutritional factors which affect the peak adult bone mass and the rates and duration of subsequent bone loss.

Early menopause is a risk factor for osteoporosis (117,118). Oophorectomized women or women with exercise-induced amenorrhea experience augmented bone loss that can be prevented by estrogen administration (119-123). Possibly, chemotherapy-induced premature ovarian failure also increases the subsequent risk of osteoporosis. Retrospective studies show that cancer patients with chemotherapy-induced ovarian failure have statistically significant decreases in bone mineral density as compared to matched controls who do not develop ovarian failure (124,125).

Chemotherapy-induced premature ovarian failure may also increase the risk of heart disease. After menopause, the rates of cardiovascular disease increase such that cardiovascular deaths are six times more prevalent than breast cancer deaths in women over the age of 65 years (31). One hypothesis for the increase in cardiovascular disease after menopause is that estrogen deficiency has an unfavorable effect on lipid metabolism (126,127). Premature ovarian failure, primarily the result of oophorectomy, appears to increase the risk of subsequent cardiovascular disease, and estrogen replacement therapy may diminish the increased risk of cardiovascular disease in oophorectomized women (74,75,128).

The risks of osteoporosis and cardiovascular disease can be diminished by estrogen-replacement therapy. Estrogen replacement is routinely administered to women with premature ovarian failure and attenuates bone loss in Hodgkin's disease patients with chemotherapy-induced ovarian failure (125). However, estrogen use in breast cancer patients is controversial and not generally recommended (129,130). An ongoing randomized trial of estrogen-replacement therapy in postmenopausal breast cancer patients is described elsewhere in this monograph.

The effects of tamoxifen on the skeletal and cardiovascular systems may be similar to estrogen-replacement therapy. Tamoxifen does not accelerate bone resorption and may prevent bone loss in breast cancer patients (109,131,132). In a recent randomized, placebo-controlled trial, tamoxifen treatment prevented bone mineral loss in the spine and was associated with significant decreases in indices of bone turnover in postmenopausal breast cancer patients (133). Tamoxifen also lowers total cholesterol and low-density lipoprotein levels in postmenopausal breast cancer patients (133-135). This is possibly related to the estrogen-agonist effect of the drug on hepatic lipid metabolism (133). In the clinic, tamoxifen may reduce the frequency of cardiovascular disease in postmenopausal breast cancer patients. Statistically significant decreases in cardiovascular morbidity and mortality have been observed in tamoxifen-treated patients in two large adjuvant tamoxifen trials (136,137).

The premature ovarian failure experienced by breast cancer patients may have profound consequences. Menopausal symptoms and the loss of reproductive potential may affect quality of life long after successful breast cancer treatment. Possibly, excess morbidity and mortality from increased rates of osteoporosis and cardiovascular disease will also be observed in breast cancer patients with chemotherapy-induced ovarian failure. The routine use of adjuvant chemotherapy in breast cancer patients with favorable prognoses should stimulate studies to estimate the potential adverse health effects of premature ovarian failure on the skeletal and cardiovascular systems. Importantly, tamoxifen may reduce the risks of osteoporosis and cardiovascular disease. However, more studies are needed before tamoxifen can be recommended as a preventative for osteoporosis or heart disease.

Future Research in Treatment-Related Events

Much of the current emphasis in adjuvant chemotherapy trials is on increasing the drug dose, now that there are numerous ways to augment the bone marrow recovery. The total doses of alkylating agents in standard adjuvant regimens are associated with extremely small risks of ANLL and no apparent increase in the risks of second cancers. Whether the same is true of the more dose-intensive adjuvant chemotherapy regimens now being tested remains to be determined. If the promise of prolonged survival with high-dose chemotherapy is realized, possibly unique, and as yet unanticipated, treatment-related events may occur.

Carbustine, a drug that produces acute pulmonary toxicity, was unexpectedly associated with the development of symptomatic pulmonary fibrosis between 7 and 12 years after its administration to children (138). High-dose chemotherapy containing carbustine is currently used in high-risk node-positive breast cancer patients, and pulmonary toxicity is a frequent side effect (130). Delayed pulmonary toxicity, if it occurs, could result in morbidity, or perhaps mortality, in patients who survive breast cancer. Long-term follow-up studies are critical to the evaluation of possible adverse treatment-related effects of high-dose chemotherapy.

How adjuvant chemotherapy affects cognitive and neuropsychiatric function is another area of potential importance. In a small uncontrolled pilot trial, moderate impairment in a variety of neurophysiologic tests was observed in breast cancer patients recently treated with adjuvant chemotherapy (140). Larger studies with appropriate controls are required to determine whether adjuvant chemotherapy affects cognitive function.

The benefits of adjuvant therapy are well established. Ongoing research is dedicated to improving the efficacy of the treatment and identifying which patients are most and least likely to benefit from the treatment. The long-term survivorship of breast cancer patients justifies parallel research efforts to identify and quantitate treatment-related events and how these may affect quality of life.

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Breast Cancer and Pregnancy

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Breast cancer treatment during pregnancy involves a host of psychosocial, ethical, religious, and even legal considerations, as well as medical multidisciplinary decisions, since the effect of treatment on the fetus must be considered. For example, breast or chest wall radiotherapy should be avoided. The absorbed fetal dosage is at least 5 cGy early in pregnancy and increases to several hundred cGy late in pregnancy to the fetal part immediately below the diaphragm. In the second and third trimesters, chemotherapy is associated with intrauterine growth retardation and prematurity in about half of the babies; the risk of birth defects is a concern in the first several weeks. Typical anesthetic agents readily reach the fetus but are not known to be teratogenic. Although abortion will allow full and comprehensive treatment to the mother, it is not known whether the procedure itself is therapeutic. Early in pregnancy, abortion deserves strong consideration, since the effects of treatment on the fetus will not be a consideration. The poor prognosis of pregnancy-associated breast cancer in the past is probably attributable to a combination of initial delay of diagnosis and possibly to unfavorable biologic characteristics of the hormonal milieu of pregnancy. When pregnant patients are matched stage for stage with controls, survivals seem equivalent, although pregnant patients present with more advanced disease. [Monogr Natl Cancer Inst 16:113-121, 1994]

Incidence

Pregnancy-associated breast cancer seems to have become increasingly common in the past several years, perhaps because more women are presently pregnant in their 30s and even 40s and because breast cancer incidence increases with age. Women who are pregnant at an older age may also have more breast cancer risk factors. These include being white, college educated, and socioeconomically privileged and having had a late first full-term delivery. Additionally, there has been an increase in breast cancer incidence in all age groups over the past several years.

This report and almost all others traditionally consider breast cancer as associated with pregnancy if the initial diagnosis was made during pregnancy or within 1 year afterward. The reported incidence in 32 series over the past several decades, reviewed by Wallack et al. (1) ranged from 0.2% to 3.8%. Nevertheless, ignoring the common definition of pregnancy-associated breast cancer, the number of patients who had a breast cancer while pregnant is much higher, given that the occult preclinical tumor

growth phase is several years (2,3). Diagnosed breast cancers occur in between 1:10 000 and 1:3000 pregnancies (4-6), making the malignancy about as common as that of the uterine cervix (7). The incidence among breast cancer patients less than 40 years old is at least 15% (1,8). One investigator (9), noting an even higher coincidence among young women, has reported that 10% of 67 patients less than 35 years old were pregnant at the time of diagnosis and that an additional 15% had been pregnant within the previous year. The average age of patients with pregnancy-associated breast cancer was between 32 and 38 years (1). Birks et al. (10) described a 16-year-old with pregnancy complicated by breast cancer, and the youngest reported with metastatic breast cancer during pregnancy was 18 years old (11).

Diagnosis and Delay

A thorough breast examination is especially important at the first obstetric visit, since with the progression of pregnancy there is increasing firmness, nodularity, and hypertrophy, which may obscure a subtle mass lesion. As the pregnancy continues, masses may feel similar to the thickness produced by normal hypertrophy, creating the illusion that they have resolved. Needless to say, the finding of a breast mass during pregnancy mandates a somewhat different plan of action than in the nonpregnant young woman. In the menstruating woman, one might wait and re-examine the patient just after her next menstrual period(s). In the pregnant woman, no cycle exists, and the hormonal milieu intensifies week after week.

Mammograms are not routinely performed, since little information can be gained. The hyperemia and increased water content of the breasts during pregnancy contribute to a generalized radiographic density, with loss of the contrasting fatty tissue that usually helps to define tumor masses (12). There is virtually no ionizing radiation to the fetus, especially if the abdomen is shielded. On the other hand, depending on the individual circumstances, mammography may be useful. In one series, negative mammograms were found in six of eight pregnant patients with a breast mass and subsequent biopsy-proven cancer (13). Breast ultrasonography should be accurate and safe, as it is in nonpregnant women, in differentiating cyst from solid in a palpable mass.

Aspiration of a mass with a fine needle and its disappearance readily serve to differentiate a cyst or galactocele from a solid tumor. Fine-needle aspiration cytology does not have the same

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accuracy during pregnancy as it does in the nonpregnant state. The hyperproliferative cellular state of the mammary tissue leads to the possibility of a false-positive diagnosis of malignancy. An experienced aspiration cytopathologist with knowledge of the clinical setting is required to differentiate the atypical cytomorphic features seen in benign tissue during pregnancy and especially fibroadenomas from malignancy (14). As in nonpregnant patients, the needle technique runs the risk of missing the mass unbeknownst to the surgeon. Excisional biopsies under local anesthesia during pregnancy may be difficult, due to the hypervascularity and edema, but are necessary. An incisional biopsy can be an alternative, although the inherent problems are similar.

Benign lesions during pregnancy, in decreasing order of frequency, include fibroadenomas, lipomas, papillomas, fibrocystic disease, galactoceles, and inflammatory lesions (15). In a series by Byrd et al. (16) of 105 benign biopsy specimens, 71% of patients had conditions also found in nonpregnant women, and 29% had changes peculiar to gestation, such as lobular hyperplasia, galactocoele, lactational mastitis, and so on. Moreover, localized breast infarcts can cause mass lesions during pregnancy, either from overgrowth of a pre-existing fibroadenoma (17) or spontaneously (18,19).

Inflammatory cancer probably arises no more frequently in pregnant patients than in others (1,20), despite earlier opinions to the contrary (4,21). Notwithstanding referral patterns that might attract more severe cases, only 3% of pregnant patients with breast cancer at Memorial Hospital had inflammatory breast cancer (22). Nevertheless, the surgeon must not make the dire error of mistaking inflammatory cancer for the quite common lactational mastitis or abscess (23). White (21) made the simple suggestion more than 30 years ago to perform a biopsy on all lactational abscesses at the time of incision and drainage.

The advanced disease and poor prognosis, often characteristic of gestational breast cancer, have been attributed by many authors to the delay of diagnosis. Delays of several months or more after discovery of a mass and before biopsy are common (8,24-27). A study of 63 breast cancer patients, who were referred to Memorial Hospital between 1960 and 1980 and diagnosed while pregnant or 1-year postpartum, seemed to reveal particular reluctance toward performing a biopsy during pregnancy (22). Less than 20% of such patients were diagnosed and treated during pregnancy. Almost half were diagnosed and treated within 12 weeks after delivery for a mass noted during pregnancy. Even in those with previously undocumented masses, the large size of the cancers at the time of postpartum diagnosis (median, 3.5 cm) makes it likely that a smaller mass was palpable during pregnancy. Considering that pregnant women are in routine contact with their obstetricians, the patient is probably not responsible for the majority of delay. Probably, physician procrastination is attributable to the higher complication (bleeding, infection) rate expected in biopsies of the pregnant or lactating women (16). The likelihood of finding cancer appears to be similar to that in a nonpregnant population: Byrd et al. (16) further reported 22% of breast biopsies in pregnancies showed malignancies compared with 19% in overall patients.

Special Problems of Breast Biopsy During Pregnancy and Lactation

Biopsy of the breast of a pregnant or lactating woman calls for tedious and meticulous hemostasis because of increased vascularity and the likelihood of a postoperative hematoma. The lactating breast is prone to infection, given the good culture medium provided by milk. Anesthesia by local injection may be difficult in the depths of the enlarged breast. Local anesthesia is theoretically safer, although monitored sedation or even general anesthesia is acceptable, especially in the later phases of pregnancy (*see* "Anesthetic Considerations" section *below*). In the earlier literature, Byrd et al. (16) reported only one fetal demise in more than 100 biopsies on pregnant patients under general anesthesia. (Follow-up on the delivery and physical condition of neonates was not made.) Nevertheless, the administration of drugs preoperatively, intraoperatively, and postoperatively requires special knowledge and caution.

Since doctors and patients realize the value of a routine two-stage procedure for breast cancer, local anesthesia for breast biopsy during pregnancy seems ideal. The individualized preparation necessary before definitive treatment of breast cancer in a pregnant woman usually militates against proceeding during the biopsy procedure. A brief delay between biopsy and definitive treatment affords the surgeon time to plan with oncologic and obstetric consultation and allows the patient and her family to consider the pregnancy in light of the proposed cancer treatment.

Although excisional biopsies under local anesthesia during pregnancy may occasionally be difficult, depending on the individual breast, an incisional biopsy is also an alternative. Liberal use of electrocautery and other hemostatic techniques is necessary. There appears to be no medical contraindication to core-needle biopsy or to needle aspiration on the breasts of pregnant women, although such techniques may be less accurate during pregnancy (28).

Because of the risk of infection and milk fistula, the patient should cease lactating before biopsy is performed. Binding the breasts and using ice packs while ceasing to breast feed may be folkloric but certainly cannot do any harm. Some kinds of hormonal manipulation for "drying up" breast milk, such as lowering the level of prolactin by the use of bromocriptine, have not been associated with breast cancer (6). If a woman will not stop nursing but will accept the risk of fistula or infection (best recorded in writing), the surgeon can proceed with a biopsy, depending on individual factors such as depth and central position of the lump, etc. Although there appear to be no data on the subject, it is surmisable that the risk of milk fistula increases from low in peripheral biopsies to high in central biopsies. Infection is more common, due to milk being an excellent culture medium. Since the large ducts intercommunicate, the septic process can easily involve the whole breast and can become a life-threatening infection.

Concerning infection, if the woman stops nursing for 1 day, a dose of some preoperative prophylactic antibiotic can be given. The milk, containing the mother's antibiotics, can be pumped as completely as possible during this period and discarded. After a

brief period of bottle feeding, the infant may then resume breast feeding, assuming a benign diagnosis.

Considerations of the Developing Fetus Regarding Irradiation

In cancer diagnosis and treatment, dangers to the developing fetus include those influencing development, such as the teratogenicity caused by radiation, chemotherapy, and general anesthesia. In addition to possible congenital abnormalities, various other risks such as prematurity or intrauterine growth retardation resulting in low birth weight and possible postnatal neoplasia must also be considered.

Radiation Risks

Experimentally and in humans, the principal effect of radiation during the preimplantation period (from conception to days 10-14) is embryo death. The second period, that of organogenesis (lasting from days 10 to 14 through the eighth week), is undoubtedly the most sensitive to ionizing radiation. There is a 20% incidence of severe malformations (often involving the central nervous system) in mice with exposures as low as 18 cGy and a 100% incidence with 200 cGy (29). In the pregnant women of Hiroshima and Nagasaki, an air dose of 1-9 cGy during weeks 6-11 of pregnancy resulted in an 11% incidence of microcephaly and mental retardation in children, compared with 4% in a Japanese nonirradiated control population (30).

Radiation exposure during the fetal period of gestation (from 8 weeks to term) is much less likely to produce congenital abnormalities than during the organogenesis period. In humans, microcephaly has been observed after radiation exposure during the early fetal period, but, dose-for-dose, the incidence is four to five times less than after exposure during the earlier organogenesis period (30). After about 30 weeks of gestation, radiation-induced congenital defects are extremely rare (31).

Accordingly, the atomic bomb experience and animal experimentation urge the conclusion that 5 cGy is the dose level for early pregnancy at which radiation-induced anomalies become meaningful. The American Academy of Pediatrics (1978) and other organizations support the conclusion of the American College of Radiology that interruption of pregnancy is not routinely recommended if the fetus was exposed to less than 5 cGy (1). Even low doses could have genetic effects that will be manifested only in subsequent generations derived from this offspring. The International Commission on Radiological Protection has proposed a total risk value of genetic effects of 200 per 1 000 000 per rem for all generations after irradiation of either parent (32).

Some retrospective studies indicate an association between prenatal x-ray exposure (usually via maternal pelvimetry) and future childhood cancers of the offspring. The reported risk of leukemia at 10 years, following a 2-cGy exposure, is 1:2000 versus 1:3000 in unexposed controls (15).

Staging Procedures During Pregnancy

Accurate staging and appropriate treatment depend on comprehensive evaluation for metastatic disease, and most tests use

ionizing radiation. Published estimates of the approximate fetal and maternal exposures are available (33). The radiation dose to the embryo, fetus, or even a particular fetal organ can also be specifically calculated by a medical physicist when the relevant parameters are known (for x-ray examinations—beam quality, kilovoltage, exposure time, distance, film size, view, etc.; for nuclear medicine procedures—type of agent, total activity, target organ, effective half-life, etc.) (34).

Some guidelines can be made for recommended staging tests. There is no contraindication to a chest x ray, which is sometimes performed with abdominal and pelvic shielding. Late in pregnancy, with the gravid uterus directly under the diaphragm, fetal shielding would obscure the lower lung parenchyma. Nevertheless, exposing the third-trimester fetus to the small radiation dose of a chest x ray should be of little concern. Regarding evaluation for bone metastases, serum alkaline phosphatase can be elevated due to pregnancy itself. Conventional radiography, excluding the pelvis and lumbosacral spine, can be performed (e.g., skull, long bones) with shielding.

An article notes modification of the bone scanning technique for pregnant patients (35). However, the bone scan may be deleted from preoperative staging in many individuals, since data gathered from 12 studies have shown only a 3% true-positive yield in stage I, 7% in stage II, and 25% in stage III (36). If the bone scan result will not change the immediate treatment, as is usually the case, it should be delayed until after delivery.

Magnetic resonance imaging (MRI) is the new imaging modality that is highly accurate and seems to be safe for the fetus. There are now studies of its usage for fetal imaging in prenatal diagnosis, with some follow-up of the infants (37). It will be particularly useful for the diagnosis of bone metastases, liver metastases, or even brain metastases (although a head computerized tomogram with abdominal shielding should yield only small amounts of fetal exposure).

As always, the physician must balance the fetal exposure to radiation, or any unknown effects of a high magnetic field, with each test against the probability of the test results changing the clinical management for the mother.

Breast Preservation in the Pregnant Woman

It is important to discuss breast preservation with radiotherapy as an alternative to mastectomy in all women. The fetal dose can be estimated by thermoluminescent dosimeters placed in an anatomical phantom shielding. However, as explained below, the standard breast radiotherapy course of about 5000 cGy will usually expose the fetus to from 10 cGy early in pregnancy to 200 cGy or more late in pregnancy; therefore, breast radiotherapy should be avoided as a treatment option in those currently pregnant.

The developing fetus receives from several tenths of a percent to several percents of the total breast dose. The radiation leakage from the radiotherapy unit should not exceed 0.1% of the direct beam-exposure rate, as measured at a distance of 1 m from the radiation source (38). External scatter occurs due to the collimator and blocks as well as other objects. A larger amount of radiation, however, reaches the fetus from internal scatter by the mother's tissues (which cannot be reduced by external shield-

ing). The quantity of such radiation depends on 1) the distance of the fetus from the field center, 2) the field size, and 3) the energy source of the radiation. For example, a 6-meV linear accelerator produces less fetal dose by internal scatter than a 1.25-meV cobalt-60 unit.

When the fetus is less than 12 weeks (i.e., is still in the true pelvis and perhaps 40 cm from field center), the dose from a field that is 10 cm \times 10 cm and is produced by a 4-meV unit would be in the range of 0.2%-0.3% of the tumor dose. This results in 10-15 cGy early in pregnancy for a breast treatment course of 5000 cGy. Toward the end of pregnancy, if a fetal part is 10 cm distant, it could receive more than 200 cGy for the same treatment course.

Much of the information concerning radiation therapy (and also chemotherapy) must be obtained in reports concerning lymphoma and leukemia. A report from the M. D. Anderson Cancer Center (39) discussed 14 Hodgkin's disease patients who had neck and mediastinal radiation of 35-40 cGy, while in the second and third trimesters. This is about two thirds of the dose necessary for breast cancer. With specialized techniques, they were able to keep the total estimated mid-fetus dose down to 1.4-13.6 cGy. The dose to the closest fetal part was not estimated. In the changing field of radiation therapy technology, perhaps breast radiotherapy of pregnant women will be recommended in the decades to come.

Likewise, radiation after mastectomy involves similar doses to the chest wall and poses the same hazard to the fetus. Irradiation in stage III and stage IV is often indicated because of the high risk of local recurrence. Nevertheless, it is probably wisest to delay the radiotherapy until the patient is no longer pregnant. If there is a recurrence before delivery, it could be excised to the extent possible to enable further postponement of irradiation at least until late in pregnancy, when fetal risk is greatly lessened.

To accomplish breast preservation in the pregnant woman, the plan of lumpectomy during pregnancy followed by radiation therapy after delivery has been suggested. To advocate this approach, one must extrapolate from the data of local and systemic recurrence obtained in the nonpregnant woman. However, the pregnant woman's breast, with the large interanastomosing ducts and sizable lymph/blood vessels, is not anatomically and physiologically similar to the less active breast of the premenopausal young woman. The duct structure itself might even predispose to local recurrence. At any rate, it is not certain that the same excellent results after lumpectomy and irradiation in the nonpregnant woman will necessarily occur with this treatment plan in the pregnant or postpartum woman.

Chemotherapy

Chemotherapeutic agents are minimally selective and usually affect rapidly proliferating cells, which makes the developing fetus a prime target for teratogenesis. The fetal effect is related to drug dosage, to gestational age, to synergism when combined with other drugs or radiation, and to the individual drug, working through different mechanisms and at different molecular sites. As Garber (40) states in her 1989 review, "the teratogenic effects of the approximately 20 cytotoxic agents in general use must be extracted from more than 300 anecdotal reports and in-

terviews." Most reports involve leukemia and lymphoma (41-48).

The placenta may create a biologic barrier for some antineoplastic agents (49), although most apparently readily traverse the placenta (50). There are several excellent reviews of fetal effects (40,51-54). For chemotherapy administered during the first trimester, Schapira and Chudley (55) reviewed eight reports with 71 patients and found an aggregate fetal malformation rate of 12.7%. Nevertheless, in the Sweet and Kinzie series (51) [and one other (53) just as large], about 40% of infants exposed to chemotherapy in utero were of low birth weight, and the concern is thus one of future slow development. A 1992 report (56) noted statistically significant lower birth weights than matched controls, due to both significantly lower gestation age and substantial intrauterine growth retardation. Even the infants born markedly underweight and/or premature have been called "normal," although this term lacks definition.

Adjuvant chemotherapy is the standard of care for premenopausal systemic breast cancer patients with axillary nodal metastases, and there is general agreement that patients with tumors greater than 1 cm, who have no axillary node metastases, also benefit. Even if effects of the fetus could be ruled out, any course of chemotherapy during pregnancy is serious for many reasons, including the possible complications of sepsis and hemorrhage during unplanned labor and delivery. For all of these reasons, one might consider a delay of several weeks to allow a pregnant woman to deliver before the initiation of chemotherapy. Such delays are found in nonpregnant women with postsurgical complications and with the use of radiation therapy sequentially before chemotherapy (57). The greatest permissible time lapse before effective adjuvant chemotherapy is not known. Adjuvant chemotherapy in the pregnant woman must be resolved on a patient-by-patient basis.

Metastatic Disease in the Fetus and Placenta

Only melanoma, leukemia/lymphoma, and one hepatocellular carcinoma have been reported to cause actual fetal metastases, which may suggest specific capabilities of these malignancies (58,59). Placental metastases have been reported in more than 50 patients with solid tumor, including several breast cancers, according to a review article (60). Following delivery, the child remained healthy in each case. Microscopic examination of the placenta, especially of the intervillous space, is important since only half the patients had visible metastases (61).

Anesthetic Considerations

General anesthesia is necessary for a mastectomy or axillary dissection and rarely for an adequate wide excision. There is a great deal of experience with anesthesia for the pregnant patient undergoing nonobstetric surgery, since 50 000 women per year (1.5%-2% of pregnant women) receive an anesthetic for a surgical indication unrelated to delivery (62). General anesthesia during pregnancy is difficult because of increased blood volume, increased heart rate and cardiac output, increased platelet count and fibrinogen level, supine positional hypotension, decreased pulmonary functional residual capacity, elevated

diaphragms, prolonged gastric emptying, hypervascularity of the respiratory tract mucosa, and so on. As compared with the risks of teratogenesis from radiation therapy and chemotherapy, those associated with the general anesthetic drugs are almost nonexistent. Despite the fact that nitrous oxide and halothane interfere in vitro with nucleic acid synthesis (63,64), no deleterious effects can be detected in humans (63). These potent inhalational agents have the theoretical advantage of relaxing uterine musculature and forestalling premature labor. In fact, premature labor seems to depend more on the surgical site—being more common with lower abdominal or pelvic operations—than on anesthetic technique and is not likely with breast operations. In any event, obstetricians have several drugs for reversal of premature labor. Fetal monitoring should be used whenever possible, so that patterns of fetal distress may be followed immediately by fine adjustments of anesthetic technique.

The Question of Therapeutic Abortion

The traditional view of concurrent breast cancer and pregnancy as an especially dreaded situation may have contributed to zealous enthusiasm for abortion in the past, often combined with oophorectomy. For example, Haagensen and Stout (65) recommended refusing the operation to any breast cancer patient diagnosed during pregnancy or lactation as categorically incurable (although they later changed their opinion) (66). In 1953, Adair (67) at Memorial Hospital noted longer crude survival rates associated with therapeutic abortion, especially for patients with axillary lymph node involvement (these differences were not statistically significant).

Gradually thereafter, both the opinion on the uniformly lethal nature of concurrent breast cancer and pregnancy and the unquestioned value of therapeutic abortion began to change. Holleb and Farrow (68), also at Memorial Hospital, reported in 1962 on 24 patients treated with radical mastectomy; abortion was not associated with a better survival. The most recent reports from the mid-1980s (69,70) also do not show an advantage in survival rate after therapeutic abortion, and Clark et al. (71) state in their paper that abortion may be deleterious.

In all these data, the reported number of cases in each series is small, and cases are often not staged. Most importantly, any beneficial effect of abortion may be disguised by the selection factor, since it appears that the more advanced cases may undergo therapeutic abortion that can be seen from one series that does report patient stage. For example, in a series of 63 pregnant patients of stages I-IV at the Mayo Clinic (70), 5-year survival rates of 43% were reported in the interrupted group versus 59% in the full-term delivery. A greater proportion of the stage II, III, and IV patients was interrupted. However, of the 20 stage I patients, 17 delivered and only three were interrupted. There was an excellent 5-year survival rate of 86% on the 17 stage I patients who were allowed to deliver. Only one of three interrupted stage I patients survived for a 5-year rate of 33%. However, stage I is a broad group, and most clinicians can select the ones with a poor prognosis (such as those in stage I with extensive lymphatic invasion). There may be an inclination to recommend abortion to them more readily. Similar findings in 100 cases of gestational breast cancer seen between 1926 and 1972

were published by the Petrov Research Institute of Oncology in Leningrad (72).

When combined with standard therapy, any additional benefit of routine therapeutic abortion cannot be demonstrated in these reports. On the other hand, therapeutic abortion may be strongly recommended because of the fetal damage from the proposed chemotherapy or radiation treatments. If a hormone receptor assay (by a laboratory experienced in gestational breast cancer) is positive, therapeutic abortion might also be advised. Early in pregnancy, treatment is greatly simplified with therapeutic abortion. In the end, it is the parents' responsibility to make an informed decision about continuing the pregnancy.

Treatment Delay

In view of the above, it is generally agreed that modified radical mastectomy without delay is indicated for potentially curable stages, regardless of the trimester of pregnancy or the decision for therapeutic abortion. However, Bunker and Peters (73) believed that patients whose cancer was discovered in the third trimester should be allowed to deliver before mastectomy, if the tumor was not aggressive and if a prolonged delay was not involved. Even though patients thus treated had a good survival rate in the retrospective study, this is likely to be the result of selection in that only the more favorable patients were delayed. Many other reports, including the recent ones, conclude that significant delay at any stage of pregnancy could be detrimental (22,74). With the safety afforded by advances in obstetrics, anesthesia, and surgery, significant delay before definitive surgery cannot be advocated.

Prognosis

Since the earliest reports were more than a century ago, the prognosis for patients with breast cancer during pregnancy has gradually improved. Kilgore and Bloodgood (75) in 1929 reported a 17% 5-year survival rate. Haagensen and Stout (65) reported no survivors, and White's collective series (4) showed only an 8.6% overall 5-year rate.

At about the same time, Harrington (76) at the Mayo Clinic is credited with starting to revive optimism on finding a 61% 5-year survival rate among those without axillary metastases. Unfortunately, presentation with lymph node metastases is common. Ten papers published during the 1960s (16,68,73,77-83), reporting numbers of patients ranging from 29 to 117, found a rate of positive lymph nodes ranging from 53% to 74% (median, 65%). Four similar papers (27,84-86) published during the 1970s found a rate of positive lymph nodes from 56% to 81%. Few studies have attempted to put these percentages into the context of the patient's age, referral area, calendar year, and diagnosis by designating a nonpregnant comparison group.

Fifty-six pregnancy-associated breast cancer patients (American Joint Committee stages I/II/III) diagnosed at Memorial Sloan-Kettering Cancer Center between 1960 and 1980 were compared with a consecutive mastectomy series of 166 nonpregnant breast cancer patients of the same age who were diagnosed and treated at the same hospital during the same time period by the same physicians (22). Sixty-one percent of the

pregnancy-associated patients had positive lymph nodes versus 38% of their nonpregnant counterparts ($P>.05$). Only 31% of the pregnant patients had pathologic tumors less than 2 cm versus 50% of their counterparts ($P>.05$). [The further studies on these Memorial Hospital patients are similar to other studies (8,9,70,72,79,86), which also include a "control" group.] Only four Memorial Hospital patients were lost before a 5-year follow-up and one patient before a 10-year follow-up. These five were known to have recurrent disease.

The pregnancy-associated patients with negative lymph nodes had an 82% 5-year survival rate compared with 82% in their nonpregnant counterparts. The 34 pregnancy-associated patients with positive lymph nodes had a 47% 5-year survival rate compared with 59% in their counterpart. Eleven of the 63 patients presented with technically inoperable primary tumors or distant metastases and had a median survival of 1 year. Among pregnancy-associated patients who were eligible, there was a 77% 10-year survival rate for those with negative lymph nodes and a 25% rate for those with positive lymph nodes. In comparison, the 10-year survival rate was 75% for the nonpregnant patients with negative nodes and 41% for the nonpregnant patients with positive nodes. The differences in 5- and 10-year survival times are not statistically significant.

The series of Haagensen (25), of Peters (79), and of Bunker and Peters (73) are useful because of the personally supervised treatment of gestational breast cancer and follow-up. The Peters and Haagensen series as well as four series from 1985 to 1989 (69,70,87,88) report that, stage for stage, the survival times are either equivalent between the pregnancy-associated patients and the control group, or the pregnancy-associated group has a somewhat inferior survival time (not statistically significant).

One modern series with controls (matched for age, stage, and calendar year at diagnosis) that shows a significantly worse survival for women with a current pregnancy is a report from Norway in which only three of 20 women survived more than 4 years (89). Six of 20 had negative lymph nodes. The tendency of a worse prognosis in a separate group who were lactating compared to controls was not significant. The concurrently pregnant women did not have a long diagnostic delay (2.5 months), the histologic grading was not significantly different from controls, and only two of the 20 had an inflammatory diagnosis. Therefore, there is no simple explanation for such a poor prognosis.

Another recent article from Toronto updates the M.V. Peters (73) series with the 154 patients seen between 1931 and 1985 (71), noting a 5-year survival rate of 32% at 5 years and 25% at 10 years (there is no control group). Half (50%) had positive lymph nodes, 19% had negative lymph nodes, and 31% had unknown status of their lymph nodes. These data are difficult to interpret because of the large number with unknown lymph node status, but they would not negate the premise that pregnant women present with later stage disease which is related to their poorer outcome. On the other hand, Clark and Chua (71) specifically note that there was no difference in survival with positive or negative lymph nodes.

Last, the survival results on a large population of 201 pregnant women from Argentina obtained by Lamattina et al. (90) are noted in a 1992 textbook. The pregnant women overall had a statistically significant worse 5-year survival of 51% compared

to 74% that was found in women under 40 who were not pregnant. However, as in all the other recent reports, pregnant women were diagnosed at a later stage; e.g., 58% had stage III disease versus 14% of the nonpregnant comparison group. They reported very similar survival rates of pregnant versus nonpregnant groups when the patients were compared according to stage.

Steroid Hormone Receptors

Little is known about the accuracy and ultimate value of steroid hormone receptor status during pregnancy. The results of a small collected series of 10 pregnant patients showed eight to be estrogen receptor negative, and two to be low positive (1). Pregnancy may result in false negatives in two ways: increasing estrogen and progesterone concentrations are known to down-regulate estrogen receptor levels in some cell lines (91), and thus actual estrogen receptor levels could be suppressed below a threshold detectable by the ligand-binding assay. Second, routine ligand-binding assays (without exchange techniques) depend on the availability of unbound receptor, and, in pregnancy, all binding sites may be already occupied by endogenous hormone. In the nonpregnant state, only up to 35% of cytosol receptor was occupied by endogenous steroid, so that most was available for assay (92). When the receptor assay is performed during pregnancy, unbound estrogen should first be removed by treatment of cytosol with dextran-charcoal (93). Exchange assays should then be performed to detect occupied estrogen receptor within cytosol (94) and nuclei (95). Since most laboratories are not experienced in these techniques, the frozen tissue should be shipped to a laboratory where the procedures are routinely performed. Immunohistochemical staining assays are arguably more accurate in the pregnant woman than the biochemical assay. No retrospective data on pregnant patients with accurate hormone receptor status now exist for formulating recommendations on therapeutic abortions, hormonal manipulation, or subsequent pregnancies.

Effect of Subsequent Pregnancy on Breast Cancer Prognosis

Many more breast cancer patients will be seeking medical advice about pregnancy, since oophorectomy is no longer performed adjuvantly and since more women are bearing children in later years. Even the earlier literature suggested that at least 7% of women who did not undergo oophorectomy after mastectomy have one or more pregnancies, and 70% of these pregnancies were to be expected within the first 5 years (15).

From the meager amount of literature on the topic, it has been generally observed that breast cancer patients who subsequently become pregnant survive very well, often the same or better than patients with no subsequent pregnancy (1). Eight (67%) of White's (21) patients who became pregnant lived at least 5 years, and 58% lived for 10 years. A similar finding was recorded by Rissanen (96), whose 53 patients had 5- and 10-year survival rates of 77% and 69%, respectively. Fifty percent of patients in Cheek's (97) series survived 5 years, but only 29% of the Applewhite et al. (27) series survived 5 years. Holleb and

Farrow (68) reported on 52 patients, with an overall 5-year survival rate of 52%, whereas a 75% 5-year survival rate was reported by Cooper and Butterfield (98) in 32 patients. Are these good results purely a function of selection? Medical personnel may not have warned good-prognosis patients as strenuously against pregnancy, and a personal belief in their favorable outlook may subconsciously have allowed these women to become pregnant.

The case-matching studies attempt to eliminate the obvious factor of pregnancy occurring only in those with a good prognosis. Ninety-six patients with subsequent pregnancy were matched by Peters (79) with respect to age and clinical stage. The patients with subsequent pregnancy not only had a longer survival time than those without subsequent pregnancy but also had longer disease-free intervals when cases of recurrence were compared. Furthermore, when the factor of selection through early death was minimized by considering only those who became pregnant within 6 months after mastectomy, 54% were found to have survived for 5 years. In a more recent analysis, Cooper and Butterfield (98) matched each of 40 patients who subsequently became pregnant with two controls as determined by the clinical stage, age, status of lymph node involvement, and equal survival at least to the time of pregnancy. The patients with subsequent pregnancy still had a survival time superior to that of the controls.

How much reliance can be placed on these reports? Each report probably contains a small fraction of such patients from that institution, and to base advice on such a subset can be unsound. For example, consider the series, from Memorial Sloan-Kettering Cancer Center: Over 30 years, 41 stage I and II patients were found who became pregnant after breast cancer treatment, and they had an outstanding 80% 5-year survival (99). However, based on the numbers and ages of women seen in those 30 years, as I was able to obtain from the Tumor Registry, and assuming only 7% of breast cancer patients less than 40 years became pregnant, this study should have reported on at least 450 women! Therefore, the patients reported from Memorial Hospital represent a highly selected subset, possibly 10% or so of the total who became pregnant after breast cancer treatment.

Does a good survival rate in a small subset prove the safety of subsequent pregnancy after breast cancer? I think not. Since pregnancy is not coded as a disease by the Record Room, cases over the long term are difficult to find. Most patients' names are obtained by asking surgeons for names over the decades. It appears to be human nature to remember those who have been seen more recently because they are alive. The same phenomenon seems to be noted in a recent abstract: A questionnaire survey of the French Gynecology Society of French obstetricians disclosed a total of only 68 women in all of France who had a subsequent pregnancy after breast cancer treatment (100). They had a good survival, similar to that of the control group.

In their 1989 article, Clark and Chua (71) update the patients first reported by M.V. Peters (73) in 1962. In the 136 patients, who were not compared to a control group, they found excellent survival times. They found a significantly better prognosis for the younger patients. In this report, the greater interval from treatment of breast cancer to subsequent pregnancy is highly

significant in predicting better survival, with comparisons of less than 6 months, 6 or more months but less than 2 years, and 2 or more years. Nevertheless, the question about the total number denominator of women with subsequent pregnancies after breast cancer treatment is applicable to this paper. Clark and Chua (71) comment in the introduction that "1500 new patients with breast cancer annually" were seen at their institution and one-third that number in 1958. Even though tabulation cannot be performed from these numbers, I suspect that the majority of breast cancer patients with subsequent pregnancy were not identified.

In summary, the limited literature on subsequent pregnancy after breast cancer with its highly selected patients does not allow one who reviews it to be certain about the effect on prognosis. Regarding advice to the individual patient who has decided to become pregnant, most clinicians recommend at least a 2- to 3-year delay to allow aggressive disease to become manifest. After that time interval, the rate of breast cancer recurrence is smaller and more constant, year for year.

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Section V: Reproduction, Menopause, and Hormone-Replacement Therapy

*William H. Hindle**

We have had an excellent overview of breast cancer in young women, noting that if we define young as under the age of 40, the incidence of breast cancer in this group is only 7%. However, the evaluation and treatment of these young patients reflects on all women with breast cancer.

We reviewed screening and prevention and the special considerations that are necessary because of the lack of statistical power in most of those studies on women in this young age group. We have emphasized treatment and questions of whether younger women respond differently to treatment.

We will now address reproduction and menopause, which is at the other end of the spectrum for this age group, and hormone-replacement therapy. The presenters will look at the data and give us recommendations for future research.

But first I would like to broaden the focus a bit and relate to the clinical practice of the gynecologist. As dramatic and as tragic as the diagnosis of breast cancer is to a single woman, there is a much larger problem that deals with the entire population of women who do not have breast cancer.

Early in my practice I spent most of my time, and I really mean most of my time, talking to patients about contraception, and most of that was about oral contraception, which relates to breast problems. By the time of my latter practicing years, my patients had become perimenopausal. Then, I spent my time talking about estrogen-replacement therapy, estrogen deficiency, osteoporosis, and cardiovascular disease.

The major cancer that I was involved with was, of course, breast cancer, and I became very impressed with the emotional impact of the fear of breast cancer on patients and on their physicians. I noticed that this fear translates into denial, which creates a problem with compliance, and it relates to birth-control pills and to estrogen-replacement therapy and to the education of physicians.

This fear of breast cancer—and it is the most powerful emotion I know of in all of gynecology—and its related denial affects the patient, affects her significant other, affects her family and relatives, AND it affects her physicians! The fear erects barriers to accepting information in both directions and to the physician's responding appropriately to the patient's needs as regards her breast and the possibility of breast cancer.

If you ask young patients why they don't take birth-control pills, you will find that one of the major reasons is their fear that breast cancer is related to taking birth-control pills. If you ask young patients why they don't get screening mammography, the number one answer is that their doctor didn't recommend it; number two, they are afraid something might be found and that this might be breast cancer.

Why do mammographers dictate long, confusing reports? It's because of fear of missing breast cancer. Why do primary health care providers hesitate to order screening mammography? They say things like: "...young patients don't need it.." and "...my patients are not at high risk." And, the physician doesn't understand the mammography reports and doesn't know what to do when he gets them.

So, even though we have a lot of data, we need to get this information more broadly disseminated to the public and to physicians. With gynecologists, as you know, failure to diagnose breast cancer is the leading cause of malpractice suits. However, courses given for gynecologists in breast disease are not very common, and many of those are not well attended.

If you speak to gynecologists as I do, being one of them, you find that they really don't understand breast problems. They are afraid of breast problems and do not want to get involved with something that they weren't trained to cope with. They often make statements like "I don't want to get involved." And, "I don't know what to do."

This isn't surprising! When I joined the faculty of USC Medical School 5 years ago, I asked third-year students what education they had had in breast disease. The answer was: a 1-hour lecture in the second year given by a pathologist! (At least she was a woman.) That was to be their entire education in breast disease in 4 years at medical school. Thankfully, this has now changed with our program of teaching physicians, particularly gynecologists, about breast disease.

So, what is needed and what must we do to combat this fear of breast cancer? The answer is to educate and to provide accurate information. We need to educate young women. We need to educate all women. We need to educate health care providers, and we need to educate all physicians.

I will give you an example. At Women's Hospital where I work, a county facility, we have established the Breast Diagnostic Center. Eighty percent of our patients speak Spanish only. Just the other day I was involved in the care of a 16-year-old Hispanic girl who had pain in her right breast. As we talked with her, she soon burst into tears. I asked her what she was upset about and she said, "I do not want to die of breast cancer." Patients who come into breast clinics are motivated by the fear of breast cancer and the fear of dying of breast cancer.

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We looked at our patient population in the Breast Diagnostic Center, at the last 2500 patients. It is a referral clinic; patients are referred by physicians within the L.A. County system or self-referred. Ours is the only clinic that allows direct patient referral, but they must have breast complaints, breast findings, or breast symptoms. We do not do routine examinations.

Fifty percent of our patients thought they had a breast mass, or their physicians thought so. Of those, only 50% proved to have a persistent palpable dominant breast mass. After evaluating these by breast-oriented history, physical examination, fine-needle aspiration of all palpable masses, and mammography, we

found that only 4% of the last 2500 patients that presented in our breast clinic had, in fact, invasive breast carcinoma.

There is this great mass of concerned and anxious patients, whose fear of breast cancer compelled them to fight their way through the county system, who are in need of evaluation and reassurance and education, as are their physicians.

Again, while as tragic and dramatic a single breast cancer in a woman is, it is literally the tip of the iceberg in terms of what needs to be done in educating and providing information about breast problems in forums like this and others throughout the United States.

Breast Cancer in Young Women: Effect of Chemotherapy on Ovarian Function, Fertility, and Birth Defects

Bonnie S. Reichman, Karen B. Green*

A comprehensive review of the literature was done to assess the effect of adjuvant chemotherapy for operable breast cancer on ovarian function, fertility, and birth defects. Data were limited. Cyclophosphamide, an alkylating agent, is the major cause of amenorrhea, which is due to primary ovarian failure. Ovarian dysfunction is related to age, dose, and duration of treatment. In women less than 35, pregnancy following adjuvant chemotherapy is possible. However, data are limited regarding the impact of subsequent pregnancy on the results of breast cancer. There appears to be no increased risk of teratogenesis in offspring exposed to chemotherapy after the first trimester of pregnancy. Prospective data on women who have subsequent pregnancies and on their offspring are very limited. Formation of a registry for long-term follow-up of young women detailing reproductive potential and follow-up of offspring is needed. [Monogr Natl Cancer Inst 16:125-129, 1994]

In 1948, the first description of cytotoxic-induced gonadal dysfunction was reported as caused by the alkylating agent, nitrogen mustard (1). Over the ensuing years, reports of the effects of chemotherapy on gonadal function have appeared, most frequently in the context of treatment for Hodgkin's disease, childhood leukemia, and testicular cancer, since these diseases commonly affect young people, with the majority of reports focusing on testicular rather than ovarian function. Testicular biopsy and semen analysis have provided an accurate estimation of male reproductive potential. However, the relative paucity of data regarding female reproductive potential has been due to the lack of a reliable and accessible animal model and the relative inaccessibility of the ovary to biopsy. The recording of menstrual history is a crude measure of ovarian function. Amenorrhea is not synonymous with sterility, just as menstruation does not mean that a woman is fertile. Direct comparisons cannot be made between male and female reproductive physiology, since spermatogenesis is continuous from the time of puberty and the full complement of primary oocytes is present at birth. The systemic consequences of the underlying disease may also affect males and females differently, as in the case of Hodgkin's disease in which pretreatment testicular dysfunction has been reported in as many as 30% of young males, whereas ovarian function is not clearly compromised (2). In breast cancer, the disease state in itself does not appear to impact on gonadal func-

tion. Endocrine consequences of chemotherapy also differ, depending on the cytotoxic agents, treatment dose, schedule, and duration as well as the patients' age. Extrapolations cannot be made from the experience generated from the treatment of other malignancies that affect young individuals with the effects of currently used adjuvant chemotherapy regimens administered to young women with operable breast cancer. Since more young women are offered adjuvant treatment at earlier stages of disease, the treating physicians need to be able to make accurate assessments of risks and benefits of treatment. The complex physiologic and psychosocial issues related to ovarian function in premenopausal women need to be better defined.

Normal Ovarian Physiology

A review of normal ovarian physiology is essential to an understanding of the impact of chemotherapy on ovarian function (3,4). Approximately 3 weeks after conception, the primordial germ cells arise from the endodermal yolk sac and begin migrating to the developing ovaries, where the ovaries begin to form during the fifth week of intrauterine life. During early fetal life, a complex series of cellular transformations change the primordial germ cells to oogonia and then to primary oocytes. From late in fetal life until puberty, the oocytes remain in the prophase stage of the first meiotic division. At puberty, the oocytes enlarge and the surrounding follicular layer changes to form primary follicles. From puberty until menopause, follicular growth occurs as a continuous process with ovulation in a cyclical fashion. The surrounding granulosa cells proliferate, follicular fluid accumulates, and the ovum completes its first meiotic division and is arrested in metaphase of the second meiotic division to become a secondary oocyte. This secondary, or Graafian follicle, continues to enlarge until the time of ovulation.

A single dominant follicle is selected by days 5-7 in the ovarian menstrual cycle, with ovulation of a fertilizable egg at day 14. All other follicles that were recruited in that cycle undergo

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atresia. As the dominant follicle emerges, there is increasing production of estrogen that stimulates the mid-cycle luteinizing hormone (LH) and follicle-stimulating hormone (FSH) surge. The abrupt rise in LH leads to meiotic maturation of the oocyte before ovulation, release of the oocyte by the ovulating process, and formation of the corpus luteum by luteinization of the granulosa and theca cells of the dominant follicle.

No primary oocytes form after birth in contrast to the continuous production of spermatocytes in the male after puberty. At its peak, that occurs at approximately 7 months postconception, the number of oocytes is estimated at 5-7 million. Thereafter, the number of oocytes decreases steadily by atresia. At birth, there are 2 million follicles, 200 000 remain at puberty and roughly 400 are left at menopause. Generally, only one ovum is liberated during each menstrual cycle, and since the reproductive life of a woman lasts about 30-40 years, only 300-400 oocytes mature and are extruded by ovulation. All other follicles undergo atresia.

Monthly ovulation is regulated by an intricate feedback mechanism between the hypothalamic-pituitary-ovarian axis. The periodicity of ovulation requires cyclic secretion of the gonadotropins, FSH and LH, which in turn requires pulsatile hypothalamic stimulation via gonadotropin-releasing hormone (GnRH) (4). However, gonadotropin cyclicality is predominantly influenced by ovarian estrogen and progesterone production. The normal menstrual cycle has three phases of steroid production, the follicular phase, ovulation, and the luteal phase. Serum levels of LH, FSH, and estradiol also have characteristic patterns during each stage of reproductive life: prepubertal, normally menstruating, and postmenopausal.

Fertility experts use both FSH and chronologic age to predict human reproductive potential and the success rate of new methods used in infertility management. Ovarian reserve is partially defined by the FSH concentration on day 3 of the menstrual cycle. Briefly, in the normal situation, FSH produced by the pituitary signals the ovary to develop follicles. In turn, the ovary produces estradiol, causing feedback inhibition of the pituitary that results in an FSH concentration less than 10 mIU/mL. In ovarian failure or menopause, the ovary is depleted of all follicles, and there is no feedback inhibition of the pituitary, resulting in FSH levels greater than 40 mIU/mL. In menstruating women with diminished ovulation reserve, the day 3 FSH levels range is between 18 and 30 mIU/mL.

Chemotherapy and Ovarian Function

Combination chemotherapy has resulted in long-term cures in the treatment of Hodgkin's disease, leukemia, lymphoma, testicular cancer, ovarian cancer, and breast cancer. Regimens have been designed with special care to avoid overlapping acute toxic effects. However, the long-term consequences on reproductive potential were not anticipated, most notably, when the MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) regimen was used for Hodgkin's disease (2,5). The major ovarian toxicity of cell-cycle specific agents appears to be directed at the process of follicular growth and maturation. Alkylating agents cause cytotoxicity independent of the cell cycle and affect the resting oocyte. Ovarian biopsies in patients

undergoing cyclophosphamide-based treatment reveal complete absence of ova or small numbers of inactive ova with fibrosis and no evidence of follicular maturation (2,6,7). In many cases, the histology is similar to postmenopausal ovaries. With the destruction of ovarian follicles, there is loss of steroid-producing cells. The reduction of the serum estrogen levels results in the interruption of the normal cycling of gonadotropins. Ovarian dysfunction is manifested by irregular menses, with eventual amenorrhea and development of menopausal symptoms.

Adjuvant Chemotherapy and Ovarian Function

For the purposes of this review, the chemotherapy agents that are frequently used in the adjuvant setting will be discussed in detail. These include cyclophosphamide (C), methotrexate (M), and fluorouracil (F), CMF and its variants, and doxorubicin (A), commonly combined as CAF, or AC. The alkylating agent, cyclophosphamide, is most frequently at the center of adjuvant regimens and appears to be the major cause of ovarian failure (8). Amenorrhea and infertility have not been associated with the cell-cycle specific antimetabolites, methotrexate and fluorouracil, when given in the dose ranges used for adjuvant treatment. The data regarding the anthracycline, doxorubicin, is even more limited and its effect on fertility has not been well defined. When administered, however, as part of the ABVD regimen (Adriamycin, bleomycin, vinblastine, dacarbazine) for Hodgkin's disease, there is less gonadal dysfunction than with the MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) regimen (9). Clearly, the impact of the adjuvant regimens, as they are currently administered, warrants further study.

Endocrine hormone profiles obtained from premenopausal patients treated with adjuvant chemotherapy who develop drug-induced amenorrhea are consistent with primary ovarian failure (7,10-14). Adjuvant regimens studied include "standard" CMF with oral cyclophosphamide, FAC, continuous oral cyclophosphamide with and without mitomycin, fluorouracil, and L-phenylalanine mustard. Estradiol and progesterone levels remain persistently low and cease to show their normal cyclic changes, while the pituitary gonadotropins, FSH and LH, are elevated to postmenopausal levels. Serum dehydroepiandrosterone and prolactin levels are not affected, which is consistent with intact adrenal and pituitary functions, respectively. Similar findings have been reported in Hodgkin's disease after MOPP chemotherapy and after cyclophosphamide for glomerulonephritis (2,5,6). Coincident with the endocrine profile of treatment-induced ovarian failure, patients may develop menopausal symptoms, such as hot flashes, decreased libido, changes in sleep patterns, irritability, vaginal discharge and/or dryness and dyspareunia.

The risk for developing treatment-induced ovarian failure is dependent on patient age and the total cumulative dose of drug. Generally, younger patients are able to tolerate larger cumulative doses of chemotherapy before developing amenorrhea and have a greater likelihood of resumption of menses after therapy is discontinued. Older patients who already have a depleted number of follicles at the time of exposure are more susceptible to the effects of chemotherapy.

Koyama et al. (7) demonstrated the relationship of age and dose among 18 premenopausal patients who received single-agent daily oral cyclophosphamide at 100 mg/day as adjuvant chemotherapy for operable breast cancer. All of 13 patients who were at least 40 years old developed permanent amenorrhea, and the average cumulative dose at the onset of amenorrhea was 5.2 g (range, 1.4-8.4 g). Four of five patients in their 30s developed amenorrhea that was permanent in three, and the mean dose of cyclophosphamide at the onset of amenorrhea was 9.3 g (range, 7.0-11.1 g). Five patients in their 20s (mean age, 25.4 years) received cyclophosphamide with mitomycin and/or chest wall irradiation, and three developed amenorrhea; the mean dose of cyclophosphamide at onset was 20.4 g (range, 14-24.5 g).

Dnistrian et al. (14) evaluated 26 patients, treated with "standard" CMF +/- levamisole adjuvant chemotherapy, which included 14 premenopausal women, of whom 12 developed amenorrhea. The onset of amenorrhea was accompanied by a hormonal profile similar to that seen in the untreated postmenopausal or surgically castrated control patients. There was an inverse relationship between age and the duration of treatment required to induce ovarian suppression with this regimen. Patients who were at least 40 years old developed amenorrhea within 2 to 4 months of treatment, while younger patients required larger cumulative doses of cytotoxic drugs to induce ovarian dysfunction. In fact, two patients under age 30 showed no evidence of ovarian suppression after 24 cycles (2 years) of therapy.

Bonadonna et al. (15) reported the incidence of CMF-induced amenorrhea among 549 menstruating women. Amenorrhea occurred in 54% who were less than 40 years old and was reversible in 23%. In women greater than 40, the incidence of amenorrhea was 96% and reversible in 4%. There was no difference in the duration of the treatment, 6 versus 12 months, on the incidence of amenorrhea in women greater than 40 years. However, among younger women, the patient's age at treatment was the most important factor in determining both amenorrhea incidence and reversibility.

Pregnancy After Adjuvant Chemotherapy

Approximately 50% of the patients younger than age 35 resume normal menses after completion of cytotoxic chemotherapy, and thus, may be capable of becoming pregnant and having offspring (8,15,16). Sutton et al. (17) retrospectively reviewed the records of 227 patients who received adjuvant chemotherapy with FAC who were 35 years old or younger to determine the frequency and effect of pregnancy on disease outcome. Of the 128 patients whose menstrual histories were known, 59% continued to menstruate after chemotherapy, 32% experienced temporary amenorrhea, and 9% experienced permanent amenorrhea. Of the 25 patients who became pregnant, 64% continued to menstruate regularly during and after chemotherapy, 32% experienced temporary amenorrhea, and this information was not available for the remaining 4%. In this series, 33 pregnancies occurred in 25 patients, whose median age was 28 years (range, 22-33 years) and who had received chemotherapy for a median of 7 months (range, 2-24 months). The median interval between the last dose of chemotherapy and pregnancy

was 12 months (range, 0-87 months). Ten pregnancies were terminated on the physician's advice or the patient's wishes (including four terminations for conceptions during chemotherapy), two patients had spontaneous abortions, 19 pregnancies resulted in full-term deliveries, and two patients were pregnant at the time of the report. There were no fetal malformations in the 19 offspring. These data illustrate that a significant number of patients retained reproductive potential after chemotherapy. These authors suggested that pregnancy did not impact adversely on the clinical course of breast cancer, nor did the offspring of these patients demonstrate teratogenic effects. Due to limited data, the authors were unable to assess the relationship of estrogen receptor status of the tumor and pregnancy. However, the reproductive potential of the patient population was not assessed because there were no data regarding the use of contraceptives or attempts at conception.

Reports of pregnancy after cytotoxic chemotherapy have suggested that there is no increased incidence of fetal wastage and malformations over that of the general population. However, this must be interpreted with caution just as the suggestion that disease outcome is not affected by subsequent pregnancy (18-23). Data are available for a small number of patients, a population that may not adequately represent the population at large. Moreover, since the occurrence of breast cancer during pregnancy is rare, it takes many years to accrue a series, during which time both adjuvant treatment regimens and staging systems used change. Since pregnancy is not usually case-coded as a disease in the record room, the physician's memory is often the basis for retrospective reviews. Data generated from accrual-based surveys may bear the consequence of faulty or selective memory on the part of physicians. Physician's warnings to patients with good and poor prognosis might have been different and resulted in differing attempts at reproduction and pregnancy rates in these groups. The effects of the underlying disease and pregnancy results are unknown in patients who died or were lost to follow-up. Clearly, information needs to be generated for large populations of women with similar disease and treatment profiles with regard to menstrual history, hormone levels, contraception and attempts at reproduction, and subsequent pregnancy and results.

Pregnancy During Adjuvant Chemotherapy and Fetal Results

Data are limited regarding the teratogenic and mutagenic potential of cytotoxic chemotherapy delivered during chemotherapy. Review of the literature reveals anecdotal experiences, numerous reports with single-agent chemotherapy, many of which employed doses that would be considered suboptimal by today's standards. Moreover, there are very limited data regarding the long-term follow-up of offspring who were exposed to chemotherapy in utero or conceived after chemotherapy. This would reflect germ-cell exposure, with possible direct germ-cell mutagenicity and/or toxicity. Beyond obvious malformations present at birth, special attention needs to be directed to the possible subtle as well as the delayed consequences that include impaired physical growth, intellectual and neurological function, gonadal function and reproductive capacity, transplacental car-

cinogenesis, transplacental mutagenesis of germ-line tissue, and secondary carcinogenesis. The karyotypic analysis of offspring might provide useful information. Recessive mutations may take several generations to appear. Thus, the risk to the gene pool has not been assessed.

The probability of teratogenesis during pregnancy is influenced by the trimester of exposure, the agents given, drug dose, and schedule (23-28). During the first trimester, the period of organogenesis, exposure may result in congenital malformations and/or fetal demise. During the second and third trimesters, chemotherapy may affect fetal growth and functional development, especially that of the brain, but rarely causes congenital malformations. In a comprehensive review of chemotherapy given during pregnancy, Doll et al. (24) summarized the reported cases of fetal malformations associated with treatment during the first versus the second and third trimesters of pregnancy. During the first trimester, there were 24 malformations among 139 (17%) exposed to single agents versus seven malformations among 45 (16%) exposed to combination chemotherapy. However, when chemotherapy with folate antagonists and/or concurrent radiation was excluded, the incidence for single-agent associated malformations declined to 6%. In addition, four of the seven malformations seen with combinations and one of the 24 associated with single agents were exposed to procarbazine, as part of MOPP. Of note, the incidence for major congenital malformations in the general population is 3% of all births (29). In contrast, chemotherapy given during the second and third trimesters has not been associated with an increased risk of teratogenesis (24). Antimetabolites, especially methotrexate, should be avoided throughout pregnancy. Alkylating agents appear to be less teratogenic, with six fetal malformations reported among the 50 patients exposed when given as a single agent. The effect of anthracyclines, in particular, doxorubicin, has not been clearly defined, although one case of fatal myocardial necrosis was reported with daunorubicin (30).

Mulvihill et al. (31) reported the results of a retrospective review of pregnancy outcome obtained by postal survey among female patients treated on Cancer and Leukemia Group B trials for a variety of advanced malignancies that included four patients with breast cancer. There were 133 pregnancies among 66 patients; 43 pregnancies ended before therapy (group 1); therapy was given at conception or during pregnancy in 32 (group 2), and 58 pregnancies occurred after chemotherapy (group 3). The frequencies of abnormal results were similar in groups 1 and 2, eight of 37 versus five of 22, respectively. There were eight normal offspring among 10 first trimester exposures. In group 3, conceptions occurred at a mean of 27 months after treatment (range, 2-104 months). There was an unexpected increase in low birth weight, stillborn, and premature termination of pregnancy, with no excess of congenital anomalies in the first year after chemotherapy. This reflects dysfunction in the milieu required to maintain pregnancy rather than damage to oocytes.

There are very little data regarding the effects of adjuvant chemotherapy administered during pregnancy. It has been demonstrated that terminating the pregnancy does not impact on the prognosis (20). The risks and benefits of treatment must be considered on an individual basis, with attention to the patient's personal desires and the urgency to begin chemotherapy and/or

radiation therapy, which can cause potential fetal harm. If feasible, and if the patient wishes to continue the pregnancy, chemotherapy should be delayed until after the first trimester in view of the increased risk of teratogenicity during the first trimester. Chemotherapy may be cautiously administered during the second and third trimester. However, there may be an increased risk of intrauterine growth retardation, premature labor and birth, and spontaneous abortion. Clearly, decision-making is complex in this setting. If chemotherapy is given during pregnancy, delivery should be planned when the maternal hematopoietic profile is optimal, and the fetus' blood counts should be monitored. Breast feeding is contraindicated since drugs may reach significant levels in maternal milk.

Possible Benefit of Premature Menopause on Breast Cancer Prognosis

In young women with breast cancer, disease-free and overall survival depend on the disease stage at presentation and the efficacy of adjuvant treatment. The effect of currently used adjuvant chemotherapy regimens involving higher doses for shorter duration have not been adequately assessed in terms of impact on ovarian function and reproductive potential. The issue of the possible beneficial effect of chemically induced ovarian failure on long-term survival in premenopausal patients remains controversial. The recent meta-analysis of adjuvant therapy trials indicated that this may be desirable (32). Current adjuvant protocols in premenopausal patients are addressed in this issue with the randomized inclusion of LH-RH agonists and/or tamoxifen. Thus, the proposed strategies to protect ovarian tissue from cytotoxic-induced damage, including short term use of LH-RH agonists, may not be relevant in the setting of breast cancer (33,34). This subject is discussed in greater detail elsewhere in this monograph.

Infertility Management: Are There Options?

Advances in infertility management may provide alternative methods of reproduction, including embryo cryopreservation before to cancer therapy and ovary donation (35). There is no option similar to sperm banking available for ova storage. The effect of hormone replacement for the maintenance of pregnancy as part of infertility management regimens is not known. These emerging technologies present new medical, psychosocial, ethical, and legal dilemmas.

All women who have undergone treatment for breast cancer and wish to bear offspring must face the possibility that they may not live to see their children grow up. Traditionally, physicians have recommended that a woman wait 2-5 years after treatment before considering pregnancy to allow for recurrence among the majority of women who are so destined. For many women with breast cancer who already delayed childbearing, this warning might preclude realization of their reproductive potential. This recommendation might not apply equally to all women without consideration of initial stage of disease, prognostic variables, and systemic adjuvant treatment. Several series have reported that subsequent pregnancy does not impact unfavorably on disease outcome (18-23). However, typically

follow-up is short. We are not certain whether the pregnancy-associated hormonal changes will have an undesirable effect in the population with hormone-receptor positive disease, a group who would otherwise be considered to have a more favorable prognosis. As mentioned earlier, data are limited regarding the relationship between pregnancy and estrogen receptor status of the tumor.

As the incidence of breast cancer in young women continues to rise, data regarding the impact of adjuvant treatment on reproductive potential are needed. Hopefully, improvements in early detection and adjuvant treatment will translate into increased disease-free survival. Formation of a registry for the long-term follow-up of young women detailing reproduction, disease outcome, and the outcome of offspring is needed.

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Pregnancy After Breast-Conserving Surgery and Radiation Therapy for Breast Cancer

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Since the incidence of breast cancer is increasing in young women and young women are more commonly delaying child-bearing, the issue of considering a pregnancy subsequent to the diagnosis and treatment of breast cancer is becoming more common. The impact of a subsequent pregnancy on disease progression and quality of life is, however, not well defined. We evaluated treatment outcome and quality of life among 23 breast cancer patients treated with conservative surgery and radiation among the 1624 patients treated at the Joint Center for Radiation Therapy between 1968 and 1985 who had subsequent pregnancies as compared with 23 patients without subsequent pregnancy matched by age and stage at diagnosis and time to pregnancy without recurrence. Quality of life was evaluated using two self-report measures, Ferrans and Powers Quality of Life Index and the Adaptation to Surviving Cancer Profile, and a measure of parenting stress (Parenting Stress Index). Results showed no differences in recurrence or distant metastasis between the matched groups. In addition, subjects with subsequent pregnancy perceived that family issues had the greatest impact on quality of life and were not at higher risk for parental stress due to breast cancer than the normal population. Both groups of young women perceived that they were able to adjust well after treatment. Study results are consistent with other clinical studies comparing patients with and without subsequent pregnancy who have failed to demonstrate a survival disadvantage. These studies are limited by relatively small numbers of patients, and their retrospective natures do not provide definitive resolution of the problem. They do, however, provide encouragement for women desiring to have children after breast cancer treatment. These concerns about pregnancy after breast cancer treatment need to be balanced against important quality of life issues. Health care providers caring for these patients need to be prepared to discuss these risk/benefit considerations in helping patients to make reasonable decisions. [Monogr Natl Cancer Inst 16:131-137, 1994]

The decision whether to become pregnant and have a child after breast cancer treatment has become a more common clinical concern. Some women may have been attempting pregnancy at the time of breast cancer diagnosis and are eager to start a family. Others may have had future plans for children and feel ready to start a family after successfully completing treatment. A key point is that for many women and their spouses or sig-

nificant others, family issues become a very important aspect affecting their quality of life after breast cancer.

The purpose of this study was to (a) evaluate the influence of pregnancy on treatment outcome in women receiving breast-conserving surgery and radiation therapy for breast cancer and (b) assess perceptions of quality of life among young women having children after breast cancer treatment. A case-matched comparison of 23 women with and without subsequent pregnancy after breast cancer was matched with respect to age, stage of disease, and time interval from end of treatment to onset of pregnancy. Patient records were reviewed for selected demographic, clinical, treatment, and outcome variables. In addition, a mailed survey of two quality of life self-reports and a measure of parental stress were completed by subjects.

Background

Pregnancy after breast cancer is a significant concern among young women. The relative magnitude of this contemporary clinical issue is reflected in two epidemiological and lifestyle trends. First, the incidence of breast cancer continues to rise among all age groups. One hundred eighty-two thousand cases of breast cancer were projected to develop in 1993, of which approximately 20% would occur in women of childbearing age (1). While some of the more recent increase in incidence is attributed to screening mammography, breast cancer incidence has been increasing for over four decades. Age-adjusted breast cancer incidence rates continue to climb among younger women, rising from 27.5 cases per 100 000 in 1980 to 32.8 per 100 000 women in 1988 (2). Second, American women have postponed childbearing for personal, educational, and/or professional reasons (3-5). According to the National Center for Health Statistics, the rate of first births among women aged 30-34 and 35-39 increased by 140% and 124%, respectively, in the 16-year period from 1970 to 1986 (6). The rate of first birth for women over age 40 has essentially remained the same. Thus, coupled with the rising incidence of breast cancer in young

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See "Note" section following "References."

women, is the greater likelihood that young women have not started or completed their childbearing (7).

Studies of Pregnancy After Breast Cancer

While pregnancy after breast cancer is thought of as relatively contemporary consideration, the first report of pregnancy after breast cancer was published as early as 1937 (8). From 1910 to 1933, over 4000 cases of breast cancer were treated at the Mayo Clinic. Thirty-nine patients between the ages of 18 and 44 gave birth between 11 months and 12 years after mastectomy. Fifty-four percent had no axillary node involvement. Results showed a 61% 5-year survival that was consistent with survival of other women not having subsequent pregnancy. Since this first published report, several retrospective series on pregnancy after breast cancer have been reported and have not demonstrated a survival disadvantage with pregnancy subsequent to mastectomy for breast cancer (9-15). Eight retrospective series conducted from 1965 to 1986 reporting on a total of 465 women having pregnancies after mastectomy were reviewed by Danforth (16). Subjects had no evidence of disease after treatment and prior to pregnancy. Overall, 5-year survival rates were consistent across studies (mean, 71%; range, 52%-78.5%) and were comparable to survival rates in other studies of stage I and II breast cancer. Twelve studies conducted from 1946 to 1989 that included 563 patients also had an analysis of survival based on lymph node status (16). Patients with node-negative disease had an 85% 5-year survival (range, 64%-98.5%) compared with a 51% 5-year survival for patients with positive axillary nodes (range, 25%-85%). These studies suggested that survival based on stage of disease was similar for patients with and without subsequent pregnancy (17-25).

To control for a possible selection bias where pregnancy may have occurred primarily in women with less aggressive disease, two series reported case-matched comparisons based on age, stage of disease, and time from diagnosis to pregnancy (24,25). Peters and Meakin (24) matched 60 patients with stage- and age-matched controls; Cooper and Butterfield (25) matched 32 patients with two stage- and age-matched controls. Both study results demonstrated comparable 5-year survival rates between the two groups. Peters suggested that pregnancy may even have a protective effect against subsequent recurrence (24).

Influence of Other Pregnancy and Timing Factors

The number of subsequent pregnancies, timing of pregnancy after treatment, and termination of pregnancy also have been examined with regard to their influence on survival (16). Four series reported an 8%-35% incidence of multiple pregnancies after breast cancer (17,19,21,25). Five-year survival among women having more than one full-term pregnancy was comparable to that among women with single full-term pregnancies. Clark and Reid (21) reported that women having more than one full-term pregnancy had better survival than others having single pregnancies. These studies suggest that multiple full-term pregnancies after breast cancer were not associated with an increase in recurrent disease. Timing from treatment to pregnancy has been an important consideration. Young women have been

advised to wait at least 2-5 years after completing breast cancer treatment before attempting pregnancy. However, there are few reports supporting minimum and maximum waiting times. Of three studies reporting on timing of pregnancy after mastectomy, only one found that women who became pregnant within 6 months had poorer survival than women who waited longer than 1 year [53.8% versus 78%] (21). The authors suggested that a minimum of at least 1-year wait is advisable. It also has been suggested that there is little benefit using a 2-year waiting period for women in their early forties (16). The longer the waiting period, the less likely they will be able to conceive based on age alone. On the other hand, women who defer pregnancy for a longer time period have also remained disease-free during such time and may, therefore, have been demonstrated to have less aggressive tumors. Thus, the timing of pregnancy after treatment remains a difficult decision in which many personal and clinical factors need to be weighed. In most cases, it is prudent to wait 1 year.

Suggestions to terminate pregnancy were routinely recommended, despite no evidence of disease. However, termination of pregnancy does not appear to improve survival (16). Based on this information, terminating a pregnancy for purpose of disease prevention does not seem justified.

Summary of Studies of Pregnancy After Breast Cancer Studies

These studies of pregnancy subsequent to mastectomy have not shown a survival disadvantage. The number of pregnancies, timing of pregnancy, and/or termination of pregnancy also have shown little effect on survival. These studies were conducted primarily on young women with early stage I and II disease, with good prognosis. Few recommendations were made for women with advanced-stage disease. Furthermore, the studies suggested that strength and desire for children and family, attitudes of the woman and spouse or significant other, and psychosocial and quality of life issues were equally important concerns in decisions about pregnancy after breast cancer. However, no descriptions of these quality of life issues were included in the analysis. In addition, these studies all reported on survival after mastectomy.

Pregnancy After Treatment for Breast Cancer at the Joint Center for Radiation Therapy (JCRT)

This study was undertaken to examine the experience of pregnancy after breast cancer among young women treated with radiation therapy at the JCRT in Boston. The purpose of this study was to: (a) evaluate the differences in the frequency of recurrent disease in a case-matched sample of women having subsequent pregnancy after conservative surgery and radiation therapy for breast cancer; (b) assess perceptions in quality of life and psychosocial adaptation to breast cancer among young women; and (c) assess perceived parental stress in women having children after breast cancer. Subjects were identified by clinicians from radiation treatment records at the JCRT. Twenty-three women with subsequent pregnancy were case-matched with respect to age, stage of disease (tumor size and number of

involved nodes), and time from the end of treatment to the onset of full-term pregnancy. In addition, four women adopted five children after breast cancer treatment, for a total of 27 women having children after treatment for breast cancer.

Methods

After obtaining approval from the institution's review board, two principal methods of data collection were used: (a) review of radiation oncology treatment records to evaluate clinical history, treatment, and follow-up status; and (b) a mailed survey of two self-report quality of life instruments—Ferrans and Powers Quality of Life Index (26,27) and Adaptation After Surviving Cancer Profile (28)—and a measure of parenting stress (Parenting Stress Index) (29). The Quality of Life Index is a 34-item weighted index of items that assess the individual's satisfaction with various dimensions of quality of life, including an evaluation of satisfaction with and importance of health, family, social well-being, and psychological well-being (26,27). The Adaptation After Surviving Cancer Profile is a 30-item self-report rating scale assessing the individual's adaptation after completing treatment for cancer (28). The Parenting Stress Index (PSI) is a 101-item 5-point Likert scale that measures the relative magnitude of stress in the parent-child system (29).

Data Analysis

Data were analyzed using SPSS-X statistical software package (30). Comparison of the incidence of recurrent and metastatic disease between the two groups was performed using chi-square analyses. The demographic data, children and pregnancy outcomes, quality of life questionnaires, and measure of parenting stress were calculated using descriptive statistics.

Results

Demographic Profile

Selected demographic variables are summarized in Table 1. Typically, young women having children after breast cancer were Caucasian (96%), married (96%), with some college education (77%), and working either full or part time (70%). Mean age at diagnosis was 30.4 years (range, 25-37) and was similar to the comparison group. The case-matched sample had a similar demographic profile, with marital status being the major difference between the two groups (38%). The demographic profile of this study group was reflective of the lifestyle changes and trends in delayed childbearing in the United States (3,4).

Table 1. Demographic profile of mothers and comparison groups

Demographic	Mothers	Case-matched group
Caucasian	96% (n = 26/27)	88% (n = 23)
Married	96% (n = 26)	38% (n = 10)
Some college education	77% (n = 21)	40% (n = 11)
Work full or part time	70% (n = 19)	44% (12)
Mean age at diagnosis, y	30.4 (range, 25-37)	
Mean age at study, y	40.8 (range, 32-48)	

Breast Cancer History

Subjects had either stage I or II breast cancer and were treated with breast-conserving surgery and radiation therapy. Eighty-two percent (n = 19) of subjects in the mother's group and 58% of subjects in the case-matched group did not receive adjuvant chemotherapy. Of the four women receiving adjuvant chemotherapy, all received doxorubicin-containing regimens. Missing data in 50% of the subjects limited meaningful comparisons in estrogen-receptor status and history of cancer in a first-degree relative (mother or sister). In the mother's group, 13% had positive receptors, 30% had negative receptors, but 52% had no reported estrogen-receptor status. The case-matched sample was equally divided between estrogen-receptor positive (23%) and estrogen-receptor negative tumors (23%). Estrogen-receptor and positive-receptor status was missing in 54% of the matched group. Thirty percent of the mother's group had cancer in a first-degree relative (mother or sister) compared with 19% of women in the matched group.

Pregnancy and Child Profile (Table 2)

Mean time to pregnancy was 30 months (range, 6-84 months). There were 32 pregnancies and 30 live births among the 23 women with pregnancy subsequent to breast cancer. One woman experienced two pregnancy losses within the first 2 years after completing conservative surgery and radiation therapy without chemotherapy. She later had two full-term pregnancies and delivered two healthy infants. With the exception of one woman who delivered a low-birthweight infant who survived, all subjects had normal full-term pregnancies. Seventy-four percent (n = 17) had one child, 22% had two children (n = 5), and 4% (n = 1) had three children after breast cancer treatment, for a total of 30 children. Twenty-nine percent (n = 8) of

Table 2. Pregnancy/child profile

Subject No.	Total No. of pregnancies	No. of pregnancies after cancer	No. of children before breast cancer	No. of children after breast cancer
103	3	3	0	3
104	2	2	0	2
105	2	1	1	1
106	2	1	1	1
107	2	1	1	1
108	2	1	1	1
109	1	1	0	1
111	1	1	0	1
112	4	4	0	2
113	3	1	2	1
114	3	1	2	1
116	2	2	0	2
117	1	1	0	1
118	5	1	0	1
119	2	2	0	2
120	1	1	0	1
121	2	1	1	1
122	2	2	0	2
123	1	1	0	1
124	1	1	0	1
125	1	1	0	1
126	3	1	2	1
127	3	1	1	1
Total	49	32	12	30

the subjects had children born prior to their breast cancer diagnosis. In the comparison group, 44% of subjects (n = 12) had children born prior to their diagnosis and 29% never had children.

In this study, four women adopted a total of five children. Reasons for choosing adoption varied. Two women developed secondary infertility after adjuvant chemotherapy. One woman never married and became a single parent. A third woman had a prior pregnancy-associated breast cancer diagnosed 6 weeks after the birth of her first child. She received adjuvant chemotherapy and continued with normal menstrual cycles after treatment. She and her spouse also chose adoption.

Lactation After Breast-Conservation Surgery and Radiation Therapy

Anecdotal reports of absent or diminished lactation in the irradiated breast among women treated with breast-conserving surgery and radiation therapy have been reported in the literature (31-36). The degree of lactation is related to the extent of radiation injury to the mammary ducts and glandular tissues (36). Generally, the usual administered radiation dose of 4600 cGy to the breast can cause ductal shrinkage, condensation of cytoplasm in cells lining the duct, atrophy of the lobules, and perilobar and periductal fibrosis (37). Thus, women receiving radiation therapy for breast cancer will generally not lactate. However, Tralins reported, in a survey of the American Society of Therapeutic Radiation Oncologist, a total of 52 pregnancies after breast-conserving surgery and radiation therapy (Tralins A: personal communication, 1993). Thirty-four percent of the sample reported lactation from the irradiated breast and 24% reported successful breast-feeding after radiation therapy. In this study, few women reported that they were able to lactate. Two women attempted breast-feeding but discontinued it due to their infant's dissatisfaction with poor milk expression. The vast majority, however, were advised not to attempt breast-feeding in the irradiated breast due to the concern over possible mastitis.

Recurrence After Subsequent Pregnancy

Data on local and distant recurrence in the mother's group are listed in Table 3. Twenty-two percent (n = 6) of women having children after breast cancer developed locally recurrent disease compared with 29% (n = 8) in the case-matched group. Mean

time to recurrence for the six women in the mother's group was 77.8 months (range, 14-132 months). Mean time to recurrence for the comparison group was 30.4 months (range, 12-67 months). The mean interval from pregnancy to recurrence was 47.2 months. One subject (No. 124) developed locally recurrent disease 14 months after initial treatment and was subsequently treated with mastectomy without chemotherapy. Twenty-two months after recurrence, she delivered a low birthweight infant. Generally, patients were treated for recurrence with mastectomy with or without adjuvant chemotherapy and had no evidence of disease at the time of this study. In the JCRT experience as well as others, local and distant recurrences appear to be greater in younger as compared to older patients (Nixon A: J Clin Oncol, in press).

Four percent (n = 1) of the women in the mother's group developed a contralateral breast cancer compared to 11% (n = 3) of subjects in the case-matched group. Time to development of contralateral breast cancer was 66 and 57 months for the mother's and comparison groups, respectively. Differences in contralateral breast cancer between the two groups were not statistically significant.

Distant Metastasis

Data were also examined for distant metastases between the two groups. Seven percent of the mothers (n = 2) compared with 15% of the comparison group (n = 4) developed distant metastases. Mean time to metastases for the mother's group was 55 months (range, 18-92 months).

Results from this comparing women having subsequent pregnancy after breast-conserving surgery and radiation therapy have shown less incidence of both recurrent and metastatic disease, although the incidence was not statistically significant. More importantly, this study of breast-conserving surgery and radiation therapy for early-stage breast cancer supported other retrospective study findings that have failed to demonstrate a survival disadvantage. In addition, young women having children after breast-conserving surgery and radiation therapy in this study had normal full-term pregnancies without complications.

Quality of Life Perceptions in Having Children After Breast Cancer

Previous studies suggested that, in addition to prognostic indicators after breast cancer, perceived quality of life, desire for children, and the degree of support from one's spouse and family were also highly important considerations in deciding to have children after breast cancer. To obtain this information, mailed questionnaires were sent to subjects in both groups to evaluate their perception of quality of life and psychosocial adaptation after breast cancer. Subjects having children after breast cancer were also asked to evaluate their perceived degree of stress in the parent-child relationship. Sixty-four percent (n = 16) of the mother's group completed and returned the questionnaires. The remaining nine subjects declined to participate in the mailed survey. Twenty-one women in the comparison group were sent mailed questionnaires. Forty-four percent (n = 11) of the comparison group completed and returned the questionnaires.

Table 3. Recurrence and distant metastasis

Subject No.	Type of recurrence	Interval to pregnancy, mo	Interval to recurrence, mo	Interval from pregnancy to recurrence, mo
103	Local breast	18	84	66
105	Local breast	29	93	64
109	Local breast	58	132	74
117	Local breast	82	108	26
121	Local breast	30	36	6
124	Local breast	36	14	
			Mean = 77.8 mo	Mean = 47.2 mo
104	Contralateral	9	66	57
126	Distant	43	92	49
127	Distant	3	18	9
			Mean = 55 mo	Mean = 29 mo

Ferrans and Powers Quality of Life Index (QLI)

This self-report measure is a 34-item weighted index that assesses the individual's overall satisfaction with and importance of quality of life on four dimensions: health, social well-being, psychologic well-being, and family issues (26,27). The range of scores for the overall QLI and each of the four subscales is 0-30, with higher scores indicating greater overall satisfaction with quality of life and the relative importance of the dimensions affecting quality of life. The mean total QLI scores and subscale scores for the two groups are listed in Table 4. The mother's group had an overall total QLI score of 23.3, with the family subscale showing the highest score of 25.4. The comparison group reported a mean overall QLI score of 22.1 that was similar to the mother's group. Perceptions of health, social and psychologic well-being, and family concerns were equally important to the comparison group. Women having children after breast cancer reported that family issues provided the greatest degree of satisfaction and importance to quality of life.

Psychosocial Adaptation to Surviving Cancer

This self-report measure is a 30-item rating scale that evaluates the individual's perception of psychosocial adaptation after surviving cancer (28). Unlike other quality of life instruments that tap quality of life concerns during the treatment period, this instrument was specifically designed to evaluate the after-treatment cancer survivorship experience with regard to the individual's ability to adapt to relationships after cancer, deal with uncertainty over one's future, and retain knowledge about their cancer and follow-up. The range of scores is 30-150, with higher scores indicating greater psychosocial adaptation to surviving cancer. Survey results showed the mean psychosocial adaptation score for the mother's group was 92 (range, 75-111). The mean psychosocial adaptation score for the comparison group was 93 (range, 68-114). Women in both groups perceived that they had adjusted to surviving breast cancer. They were able to develop relationships after breast cancer, face uncertainty over the future, and also gain knowledge about their disease and the importance of careful monitoring. These were important aspects to consider in having children after treatment.

Parenting Stress Index (PSI)

The PSI is a 101-item Likert scale that measures the relative magnitude of stress in the parent-child system (29). The PSI is a widely used scale with demonstrated psychometric properties. It contains two domains: a parent domain with seven subscales for evaluating stress and a child domain using six subscales for

evaluating stress. The normal, nonclinical range of total scores is 180-250. Scores higher than 260 indicate major stressors in the parent-child system that can place the family at risk for problematic parenting behaviors or behavior problems in the child. Sixty-six percent ($n = 16$) of the mother's group completed the PSI. This instrument was not evaluated by the comparison group. The mean scores of the mother's and normative data are listed in Table 5. Fourteen of the 16 subjects had scores within the normal range. However, two subjects had total scores greater than 260. The Health subscale of the PSI was examined as a potential source of stress, with high scores on this subscale indicating a deterioration in the parent's health (29). Only one subject scored above the normal range on the Health subscale, indicating that one's health was a source of stress in the parent-child system. She had just completed a course of chemotherapy for recurrent breast cancer. She reported that she had felt increased tension at home, was less patient than usual with her two small children, and that she had felt increased fatigue and less ability to cope with daily routines during her chemotherapy treatment. Overall, women having children after breast cancer had comparable level of stressors in the parent-child system similar to the normative sample.

Meaning of Having Children After Breast Cancer

For clinicians working with young women, the meaning of having children may be overlooked when the focus is primarily on the disease parameters. Yet, this information is vital to help clinicians understand the vast benefits considered by these young women and their spouses or significant others. In-depth interviews into the personal meaning of having children after breast cancer were conducted with 20 women in this study and is reported elsewhere (Dow K; submitted for publication). Briefly, young women were eager to resume life goals that were temporarily thwarted by their breast cancer diagnosis and treatment. While clinicians tend to focus on the pregnancy aspects and its effect on the breast cancer, young women focus on the overall

Table 4. Comparison of QLI scores

Scale	Mothers		Comparison groups	
	Mean	Range	Mean	Range
Total QLI	23.3	18.0-28.6	22.1	15.3-27.5
Health	23.3	15.5-29.4	22.1	14.6-28
Social	23.5	20.5-27.4	21.4	13.2-27.9
Psychologic	21.8	11.9-29.1	22.6	14.6-29.1
Family	25.4	8.1-30.0	22.9	13.1-30

Table 5. Comparison of mean PSI scores between mothers and normative sample

	Mothers	Normative sample
<i>Parent domain</i>		
Depression	18.3	20.3
Attachment	11.9	12.7
Restriction of role	16.6	18.9
Competence	24.3	29.1
Isolation	12.8	12.6
Relationship	17	16.9
Health	12.1	11.7
Subtotal mean	113.3	123.1
<i>Child domain</i>		
Adaptation	24.1	24.9
Acceptance	13.5	12.6
Demandingness	18.6	18.3
Moodiness	10	9.7
Distraction	22.5	24.7
Reinforces parent	9.8	9.4
Subtotal mean	97.2	99.7
Total	210.5	222.8

experience of having children of which pregnancy is a small part. Children and family issues were a high priority and were a constant thought in their minds. Having children meant many things. They felt that somehow they were "cured," that they were well enough to look forward to a future, and they felt reconnected with their peers, friends, and family. They reported placing greater emphasis on family ties and relationships that helped improve their overall perception and satisfaction with quality of life.

The experience of having had breast cancer also shaped some of their mothering experiences. The concern over recurrence, while continually present, was less evident as time progressed. Women felt they were hypervigilant about their health care and were diligent in their follow-up visits. Knowledgeable in the management and monitoring of their own disease, they were also hypervigilant and watchful over their children's health. They initially reported more difficulty in believing that their children's lumps and bruises were usual and normal and were more likely to worry that such lumps were signs of cancer. They expressed major concerns about living long enough to experience important family life events such as birthdays, vacations, high school graduations, proms, and weddings. Yet, enjoying daily routines and pleasures helped them to practice living one day at a time to the fullest. This day-to-day time perspective helped them structure their daily goals and their future outlook. Women most often reported that they gained a sense of wisdom through the experiences of surviving breast cancer and having children. Looking back over their treatment, they felt that a history of breast cancer should not preclude others from deciding against having children and that the risks need to be carefully considered with the benefits of having children. In many respects, women reported that having children helped them to go beyond the notion of survival and they felt their lives became richer and more meaningful after breast cancer.

Discussion and Recommendations

The JCRT experience with young women having pregnancy after breast-conserving surgery and radiation therapy for early breast cancer were consistent with findings from previous studies of subsequent pregnancy after mastectomy. This case-matched comparison showed no adverse clinical outcomes of pregnancy subsequent to breast-conserving surgery and radiation therapy. Furthermore, this study also suggests that the risks of recurrent disease were not increased among women having more than one pregnancy. Overall, while this and previously reported studies did not demonstrate a survival disadvantage with pregnancy, there are several inherent design limitations. All are retrospective reports with limited numbers from single institutions. Sampling was based on a combination of review of patient records and physician recall. Furthermore, even using a case-matched comparison utilizing time to pregnancy does not completely eliminate a possible selection bias so that patients with more favorable prognosis elect to become pregnant. In addition, these studies were reported over a 40-year period where significant changes in breast cancer diagnosis, staging, and treatment have occurred. It should also be noted that the present

study and other studies were limited to women with early-stage breast cancer.

While the available evidence does not suggest adverse outcomes given these limitations, it cannot be firmly concluded that *no* effect exists. It is possible that the magnitude of the pregnancy effect may be too small to detect (16). In counseling young women about subsequent pregnancy, it appears that a major consideration is the patient's prognosis. Health care providers need to discuss this explicitly with patients and their family. In general, it seems prudent to wait at least 1 year after treatment for breast cancer before attempting pregnancy. This is a period in cancer survivorship where the woman and her spouse or significant other are recovering from the symptoms and effects of treatment and when routines are reorganized in one's family, work, and social relationships. It is helpful to suggest that a waiting time is needed to regain health before attempting the physical stress of pregnancy. Beyond a year's waiting period, it is difficult to make specific recommendations. The timing of subsequent pregnancy needs to be based on a combination of personal and clinical considerations other than an arbitrary wait of 2-5 years. In all situations, the risks with recurrence and metastatic disease, occurring during the pregnancy or thereafter, need to be weighed against the benefit of having children. Finally, in the absence of recurrent disease, routine recommendations for therapeutic abortion seem unjustified based on the available information.

This study also showed that reproductive, parenting, and adoptive concerns are very important among young women with breast cancer. While many areas of quality of life are affected after treatment, it appears that family concerns and considerations still have the greatest impact in determining one's overall perception and satisfaction with quality of life. Young women have specific developmentally based concerns and are more prone to developing psychosocial difficulties as compared with older women with breast cancer. However, this study showed that they are able to adapt well to developing new relationships, gaining perspective on their disease at a young age, and to be diligent in their own health care and follow-up. In addition, while young women having children after breast cancer may have particular concerns in parenting, they were not at greater risk for parenting stress than the general population.

These findings have specific implications for clinical practice. Oncologists, nurses, and social workers need to be prepared to discuss issues related to subsequent pregnancy from a larger perspective that not only includes disease prognosis, but also from a quality of life viewpoint. Careful deliberation with regard to the individual woman's prognosis, health, well-being, desire for children, support from spouse or significant other and family, and other sociodemographic factors needs to be considered in this difficult decision-making process.

Future Directions

Up to 25%-30% of women continue to experience significant psychosocial adjustment after breast cancer (38). Young age has been identified as a major factor in the development of psychosocial adjustment difficulties. Certainly, in young women in whom reproductive issues are of major concern, this can be

one important part of adjustment after breast cancer treatment. The recent trend to increased use of adjuvant chemotherapy and adjuvant hormonal therapy in young breast cancer patients needs further study with regard to its effects on fertility and quality of life. Ultimately, the answer to the question "what is the effect of pregnancy on survival?" will not be definitively answered given the inherent ethical problems in using a design of randomizing women to pregnancy versus no pregnancy after treatment. An improved understanding of both prognostic factors and quality of life issues will provide us with better information to counsel young women desiring pregnancy after breast cancer in the future.

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Sex Steroids and Breast Cancer Prevention

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Mitogenesis and mutagenesis are major driving forces in neoplastic development. Little is known about important breast mutagens, but much is known about breast mitogens. "Blocking" the effect of breast cell mitogens, by reducing the actual exposure of the breast to them, is an obvious strategy for breast cancer prevention. The ovarian hormones, estrogens and progesterone, are major effective (direct or indirect) breast cell mitogens. There is overwhelming epidemiologic evidence that breast cancer risk is closely related to exposure to estrogens and progestogens. A woman's exposure to *endogenous* ovarian estrogens and progesterone is drastically reduced by the use of combination-type oral contraceptives (COCs), but the *exogenous* synthetic estrogen and progestogen in the COC effectively replace the ovarian estrogen and progesterone, so that no decrease in breast cell exposure to these hormones is obtained. Doses of estrogen and progestogen in modern COCs are close to the minimum attainable, while still retaining both contraceptive efficacy and ovarian suppression (so that endogenous estrogen and progesterone do not add to the dose of estrogen and progestogen from the COC). Considerably lower effective breast cell exposure to estrogen and progestogen can, however, be achieved by using a gonadotropin-releasing hormone agonist to suppress ovarian function and compensating for the resulting hypoestrogenemia with low-dose hormone replacement. Such a contraceptive is predicted to reduce *lifetime* breast cancer risk by more than 50% if used for 10 years and by as much as 70% following 15 years of use. Contraception represents a unique opportunity to have a substantial beneficial impact on women's health; more than 10 million women use COCs daily in the United States. The observation that users of COCs have a substantially reduced risk of ovarian and endometrial cancers must encourage the extension of contraceptive development to address the most important malignancy facing modern women, breast cancer. [Monogr Natl Cancer Inst 16:139-147, 1994]

The incidence rates of breast, ovarian, and endometrial cancers increase steeply during the premenopausal years but enter a relative plateau although at high incidence rates following menopause (1). The use of combination-type oral contraceptives (COCs) reduces the risk of both ovarian (2-4) and endometrial (5,6) cancers. The normal rate of increase with age of ovarian and endometrial cancer risk is reduced during the period of COC use. Although the normal rate of increase returns when COC use stops, the protection lasts for at least 15 years after COC use ceases (2,3,7) and a substantial *lifetime* reduction in

risk of these two cancers is anticipated (8). It appears that ovarian cancer is decreased by COCs because cell proliferation associated with follicular development or ovulation is reduced; endometrial cancer is prevented by decreasing the number of days of exposure of the endometrium to the mitogenic effects of estrogen unopposed by a progestogen. The reduced mitogenic activity most likely lowers cancer risk by decreasing the accumulation of stochastic mutations (1,6,9-13).

Unfortunately, COCs have not reduced the risk of breast cancer; although they suppress ovarian steroidogenesis, the synthetic estrogen and progestogen in the COC are *both* breast mitogens and have effects on the breast, equivalent to those of the endogenous sex steroids of a normally cycling woman (6,14). As Boone and Kelloff (15) have enunciated: "The two driving forces of neoplastic progression in an epithelium are mutagenesis and mitogenesis. . . . The major strategy of chemoprevention is to block the effects of both mutagens and mitogens." While little is known about important breast mutagens, much is known about breast cell mitogens, and it is presently possible to develop a contraceptive that should prevent breast cancer by reducing breast cell mitogen exposure during the period of contraceptive use (8,16). A contraceptive that reduced levels of the key breast cell mitogens, estrogen and progestogen, should prevent breast cancer by decreasing premenopausal breast epithelial cell proliferation to below usual rates. The contraceptive consists of the following: a gonadotropin-releasing hormone agonist (GnRHA) to completely suppress ovarian function; low-dose replacement of estrogen and possibly ovarian testosterone (T); and intermittent progestogen. A 50% *lifetime* reduction in breast cancer risk should occur following a 10-year use of the contraceptive (8,16).

Rationale for the Contraceptive Regimen

Cell Proliferation in the Human Breast

Evidence from studies of chemical carcinogenesis, molecular genetics, and epidemiology suggests that repetitive cell proliferation is central to the risk of many common human cancers (9,11,12,17,18). The breast has a tightly regulated pattern of growth that is primarily under the control of steroid hormones. The rate of cell proliferation in the postmenopausal breast is

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See "Note" section following "References."

considerably less than that in the premenopausal breast (19). In nonpregnant premenopausal women, the breast epithelium undergoes repetitive periods of cell proliferation and cell loss secondary to cyclic ovarian activity. In the terminal duct lobular unit (TDLU), cell proliferation is relatively constant during the follicular phase of the menstrual cycle. However, following ovulation, TDLU cell proliferation increases twofold to threefold over follicular levels (Fig. 1), which is likely due to progesterone produced by the corpus luteum (20-25). Consistent with the breast cell proliferative rates, the size and number of terminal ductules peak during the late-luteal phase (22). If fertilization and pregnancy do not ensue, progesterone levels fall, breast cell division decreases, and cell death by apoptosis follows (21). In women using COCs, breast cell proliferation rates are similar to usual premenopausal rates (23-25).

Proliferating cell populations are more susceptible to carcinogenic effects, and the rise in cancer risk associated with cell

proliferation is, at least in part, secondary to increased risk of mutation (9,11,12,17,18). Thus, breast cancer risk would be predicted to increase to the greatest extent during periods of exposure to both estrogen and progesterone, as in the premenopausal period or in women receiving COCs; less during periods of low-dose estrogen-only exposure, as in postmenopausal women receiving estrogen-replacement therapy (ERT) or obese postmenopausal women; and least during periods of exposure to neither hormone, as in nonobese postmenopausal Asian women.

Hormonal Risk Factors for Human Breast Cancer

The age-incidence curve of cancer of the breast (plotted on log-log scales in Fig. 2), similar to that of cancer of the endometrium and ovary, shows a distinct slowing of the rate of increase at the age of menopause (16). The age-incidence curves for these common female malignancies differ from most non-hormone-dependent adult cancers that rise continuously and in-

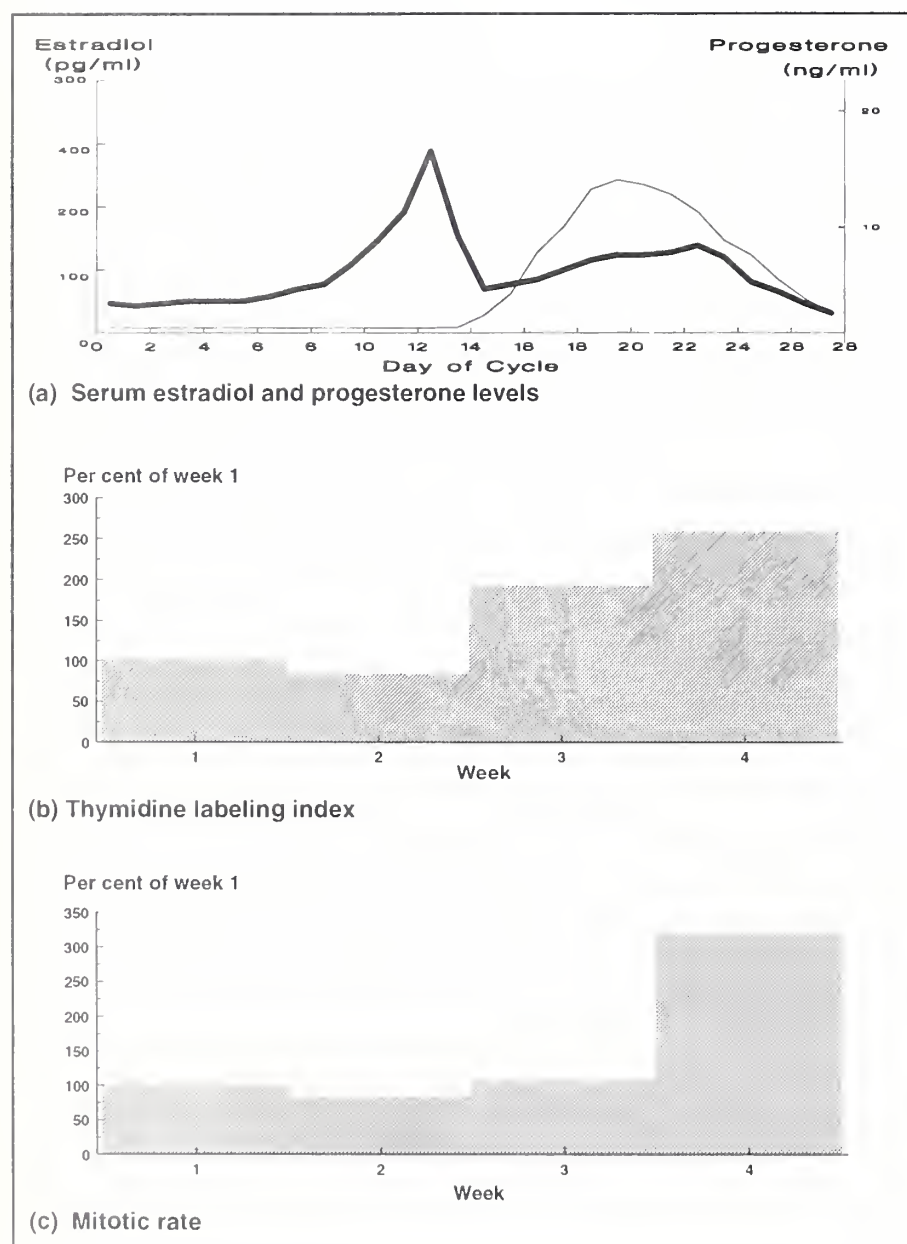


Fig. 1. Cell proliferation rates in the terminal duct lobular unit of the premenopausal breast during the menstrual cycle. (a) Serum estradiol and progesterone levels during the cycle. (b) Thymidine-labeling index by week of the cycle, expressed as a percent of week 1. (c) Mitotic rates by week of the cycle, expressed as a percent of week 1. From Pike et al. (25).

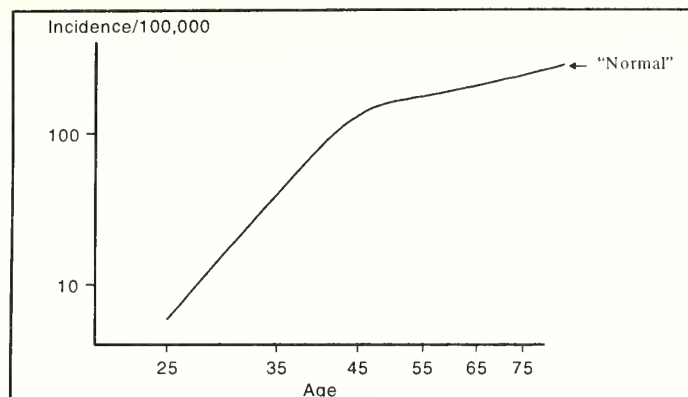


Fig. 2. Age-incidence curve of cancer of the breast. The annual incidence of breast cancer is plotted against age on a log-log scale showing a distinct slowing of the rate of increase at the age of menopause. In contrast, most nonhormone-dependent adult cancers rise continuously and increasingly rapid with age so that log-log plots are straight lines into old age.

crease rapidly with age so that log-log plots are straight lines into old age (1,26). As Fig. 2 shows, although the absolute incidence of breast cancer is higher in older women, the risk of breast cancer rises at a much slower rate after menopause. The steep rise before age 50 is, in all probability, a result of sex-steroid-driven breast cell proliferation associated with cyclic ovarian activity (*see above*). The breast cancer risk attained during the premenopausal period is not lost following menopause; this is as would be expected in a genetic multistep process (27). Following menopause, in American women, breast cancer risk rises slowly; cell proliferation rates are low (19), as there is effectively no progesterone and only low levels of estrogen. Since menopause arrests the rise in cancer incidence associated with repeated ovulation, the life-long protective effects of an early age at natural or surgical menopause (28-30) can readily be understood as reflecting an early reduction in breast mitogen (estrogen and progesterone) exposure. The data from the large case-control study of Trichopoulos et al. (28) are given in Table 1, where oophorectomy below age 35 is associated with a breast cancer relative risk of 0.36 (i.e., a 64% reduction in risk). The strong protective effect of artificial menopause (bilateral oophorectomy) shows that the association

Table 1. Effect of natural and artificial menopause (early oophorectomy) on breast cancer risk*†

Type of menopause	Age of menopause, y	Relative risk‡
Natural	<45	0.73
	45-49	0.93
	50-54	1.07
	≥55	1.48
Artificial§	<35	0.36
	35-39	0.68
	40-44	0.65
	45-49	0.73
	≥50	0.98

*2578 breast cancer patients; 2682 controls

†Trichopoulos et al. (28).

‡Expressed relative to a natural menopause at age 50.

§There were 524 breast cancer cases and 754 controls with artificial menopause.

of early menopause and reduced breast cancer risk is one of cause and effect.

Breast cancer risk is inversely related to age at menarche, because ovarian steroidogenesis, and hence exposure to estrogen and progesterone, is closely associated with menarche (31).

COCs inhibit gonadotropin secretion, thus reducing ovarian steroidogenesis, but the amount of sex steroid necessary to provide acceptable contraception in COCs appears to produce total breast cell proliferation over a menstrual cycle very close to that occurring in a normal ovulatory cycle (23-25). This suggests that COC use should not be associated with a major increase or a major decrease in breast cancer risk, as has been observed in epidemiologic studies. Meta-analyses of population-based epidemiologic studies of COC use and breast cancer risk show a small increase in breast cancer risk in young (<45 years of age) women, but no evidence of any increase in breast cancer risk with COC use in women over age 45 (6,14). Whether the increased risk seen in young women will continue as these women age is unknown (6,7,14).

Depot medroxyprogesterone acetate (DMPA) is a long-lasting (90-day) injectable progestogen-releasing medroxyprogesterone acetate (MPA), recently approved as a contraceptive in the United States. DMPA suppresses ovulation, and estradiol levels average slightly below the normal early-follicular phase level, without a preovulatory or mid-luteal phase peak (32,33). Although endogenous progesterone is completely suppressed, substantial amounts of the synthetic progestogen MPA are present. Epidemiologic studies of the effect of DMPA on breast cancer risk have found no evidence for a reduction in breast cancer risk (34,35), despite the reduction in estradiol levels, consistent with the concept that progestogens (MPA in this case) are important in the genesis of breast cancer risk.

The effect of ERT on breast cancer risk has been the subject of numerous epidemiologic studies. Meta-analysis of population-based studies shows that ERT use of 0.625 mg of conjugated estrogens (CE) approximately doubles the baseline increase of breast cancer of 2.0% per year of a normal postmenopausal woman (14,36). This is in agreement with the relative effective estradiol levels: the nonsex hormone-binding globulin (SHBG)-bound estradiol level of CE users is approximately twice that of a normal postmenopausal woman. At present, there are very few data on the effects of the addition of a progestogen to ERT on breast cancer risk. We would predict that the effects of such combined replacement therapy on breast cancer incidence will be greater than that of ERT alone; the sparse available data support this contention (37,38).

Obesity during the premenopausal years reduces breast cancer risk; premenopausal obesity considerably reduces exposure to progesterone (39). Postmenopausally, the decreased risk associated with premenopausal obesity is gradually eliminated, and an increased risk finally achieved by the increased bioavailable estrogen levels associated with postmenopausal obesity.

The incidence of breast cancer in Japan is substantially lower than in the United States. Age at menarche is later in Japan by approximately 2 years, and postmenopausal Japanese women weigh substantially less than postmenopausal women in the United States; these factors partially explain the difference in incidence (40). The low postmenopausal weight of Japanese

women will lead to low estrogen levels and, therefore, to no further increase in breast cancer risk postmenopausally as observed in Japan. In oriental premenopausal women maintaining a traditional lifestyle, urinary conjugated estrogens (41) and serum estradiol levels (42-44) are substantially lower than in women in the United States; this can account for the remaining lowered risk of oriental women (26).

A Contraceptive to Prevent Breast Cancer

It is apparent from the preceding discussion that an approach that reduced estrogen- and progestogen-induced breast cell proliferation should reduce breast cancer incidence rates. This can be accomplished by combining a GnRHA with "add-back," low-dose sex steroids. GnRHA use by women leads to a short initial agonist effect and then to suppression of pituitary, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release and thus ovarian steroid production. It was initially hoped that GnRHAs could form the basis of an improved method of contraception by offering greater convenience and effectiveness or fewer side effects than COCs. Inhibition of ovulation by the long-term administration of a GnRHA appeared to offer the greatest potential (45-47) and was found, as expected, to be dose related (48). When GnRHA is administered in a dose just high enough to ensure anovulation, the ovaries may continue to produce estrogen, but this is an unstable situation with different women having widely varying serum estrogen levels. There was concern that endometrial hyperplasia would occur in some women (49,50), while in others there would be periods of hypoestrogenemia with unacceptable vasomotor symptoms and loss of bone mineral content (48). Hypoestrogenism is invariably present when GnRHAs are given at doses to completely shut down ovarian steroid production. However, by using exogenous sex steroids, the hypoestrogenic side effects of the GnRHA can be eliminated; the dose of sex steroids needed to eliminate the hypoestrogenic effects is substantially below current contraceptive levels and below those produced by the ovary associated with repetitive ovulation.

A pilot trial was initiated with a prototype of such a contraceptive consisting of the GnRHA leuprolide acetate depot at a dose of 7.5 mg given intramuscularly every 28 days, CE at 0.625 mg orally for 6 days of 7 each week, and MPA at 10 mg orally for 13 days every fourth 28-day cycle (8,51). Twenty-one subjects at fivefold or greater increased breast cancer risk were entered and randomly assigned to treatment, 14 to the prototype contraceptive and seven to a control arm. The principal end points included tolerance of the prototype contraceptive, vaginal bleeding patterns, and the regimen's effect on the endometrium, bone, and lipids. One contraceptive subject was terminated soon after starting because of poor compliance with the CE.

Predicted Effects of the Contraceptive on Breast Cancer

To estimate the effect of the prototype contraceptive on breast cancer risk, calculations were made using a previously described mathematical model (1,40); this model accurately describes the known epidemiologic hormonal risk factors for breast cancer. The calculations are based on using the regimen at any time after the first full-term pregnancy from age 30 to 40 (8,16). The

logic of the calculations is shown in Fig. 3. Curve (a) of Fig. 3 shows the normal age-incidence for breast cancer. The GnRHA administered completely suppresses ovarian steroidogenesis; thus, sex steroid exposure is dependent on the dose of add-back sex steroids. If sex steroids were not administered, incidence rates would be equivalent to oophorectomy at age 30 rates, which are shown in curve (b) of Fig. 3. The latter curve essentially takes on the slope of the normal postmenopausal curve at age 30 rather than age 50 (average age at natural menopause). After the GnRHA alone is stopped at age 40, breast cancer risk would increase at usual premenopausal rates, as shown in curve (c) of Fig. 3. Add-back sex steroids are, however, required, and the dose of add-back estrogen must be sufficient to prevent hypoestrogenic signs and symptoms; the dose of estrogen used as postmenopausal ERT is known to be sufficient (*see below*). The effect of the add-back estrogen on breast cancer risk is assumed to be the same as that observed with postmenopausal ERT. To prevent endometrial hyperplasia and a rise in endometrial cancer risk, a progestogen must be administered (*see below*). We assumed that the effect of a 13-day progestogen regimen every fourth month on the breast is to double the effect of the ERT that is associated with the 28-day cycle in which it is administered. Our estimate of the effect of the prototype contraceptive on breast cancer risk is shown in curve (d) of Fig. 3. Table 2 shows that lifetime breast cancer risk is predicted to be reduced by almost a third if the contraceptive is used for 5 years and by more than 50% if used for 10 years. These estimates can be seen to be likely close to correct, since they are similar to the

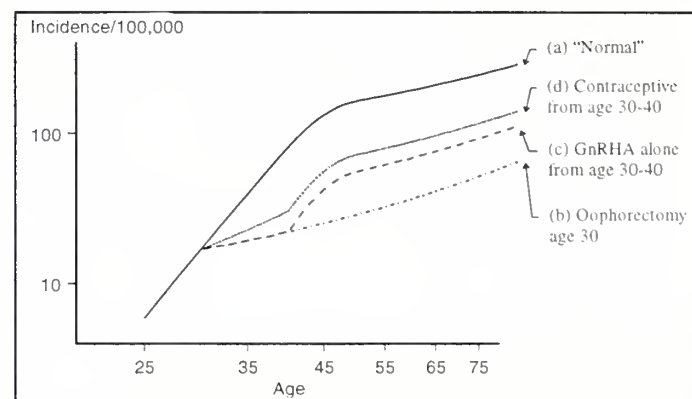


Fig. 3. Predicted effects of the prototype contraceptive on breast cancer risk. Curve shows (a) the normal age-incidence for breast cancer; (b) oophorectomy at age 30 rates; (c) effect of a GnRHA alone from age 30-40; and (d) effect of the contraceptive from age 30-40. Calculations were made according to the model described by Pike (1).

Table 2. Predicted reduction in lifetime risk of cancer with the prototype contraceptive*

Cancer	Duration of contraceptive use, y		
	5	10	15
Breast	31%	53%	70%
Endometrium	18%	33%	45%
Ovary	41%	67%	84%

* Calculations were made using the model of Pike (1) and from Spicer et al. (8), (8).

known protective effects of bilateral oophorectomy slightly modified to allow for the ERT.

Long-term studies are necessary to confirm a breast cancer protective effect of such a contraceptive approach. However, there is an urgent need to develop intermediate end points for breast cancer prevention studies, perhaps the measurement of breast epithelial cell proliferation. In our pilot trial of the prototype contraceptive, we have seen substantial reduction in radiographic densities in follow-up mammograms of some of the contraceptive subjects (Fig. 4). We have argued that these mammographic changes reflect reduced breast cell division (51).

Other Effects of the Prototype Contraceptive

Symptoms

Ovarian hormones have substantial effects on a woman's sense of well-being and the symptoms she experiences. The most dramatic examples are the symptoms occurring following the cessation of ovarian function at natural or surgical menopause (52), and similar symptoms occur with ovarian suppression by the administration of GnRHA alone to adult premenopausal women (53-56). These symptoms are predominantly secondary to the reduction in ovarian estrogens and have led, in part, to the use of ERT in postmenopausal women (57,58). In naturally menopausal women, oral estrogens such as 0.625 mg per day of CE are most commonly used.

In our pilot trial of the prototype contraceptive, a questionnaire measured both menopausal symptoms and symptoms of premenstrual distress (51). Each symptom intensity was rated and the subjects indicated the number of days each symptom occurred at each intensity level. Transient hot flashes were reported by five contraceptive subjects, were rapidly eliminated, and did not subsequently occur after the dose of CE was increased to 0.9 mg (51). Transient symptoms of vaginal dryness or painful intercourse were reported by three contraceptive subjects and two control subjects. In two of the contraceptive sub-

jects, these symptoms were eliminated when the CE dose was increased to 0.9 mg. The third subject reported this symptom complex at the start of cycle 13 when she was already receiving 0.9 mg of CE. Pelvic examination failed to reveal vaginal abnormalities, and more detailed questioning suggested these symptoms were a reflection of altered libido and were completely eliminated by the addition of a small dose of androgen (*see below*).

Fig. 5 shows the median percent change from baseline in symptom scores for individual subjects following cycles 2-6 and after cycle 12, which decreased below baseline. Comparison of contraceptive with control subjects demonstrated greater reductions in total symptom scores in contraceptive subjects that was statistically significant at both 6 months ($P = .04$) and 12 months ($P = .03$). Thus, a reduction in premenopausal estrogen levels can be accomplished without producing menopausal symptoms, provided an adequate estrogen dose is administered.

The following seven symptoms accounted for the decrease in total symptom score of the contraceptive group: abdominal bloating or fullness; abdominal cramps or pain; breast swelling; breast pain or tenderness; anxious, tense, or nervous; irritable, angry, impatient; and mood swings. These are luteal phase symptoms, and they did not improve in the control group. Progestogens, whether produced by the corpus luteum following ovulation or exogenously administered (59-61), have negative effects on symptoms. In premenopausal women, the luteal phase is associated with negative symptoms, which in the most extreme are termed premenstrual syndrome (PMS).

Bone Mineral Density

Generally, bone mineral density (BMD) remains constant throughout the premenopausal years (62,63), although in the spine it may begin to decline before menopause (64). Recent studies suggest BMD in premenopausal women is actually dynamic and related to ovarian function; pregnancy (65) and lactation (66,67) are associated with a reduction in BMD, which appears to be reversible (67,68). BMD declines with the use of

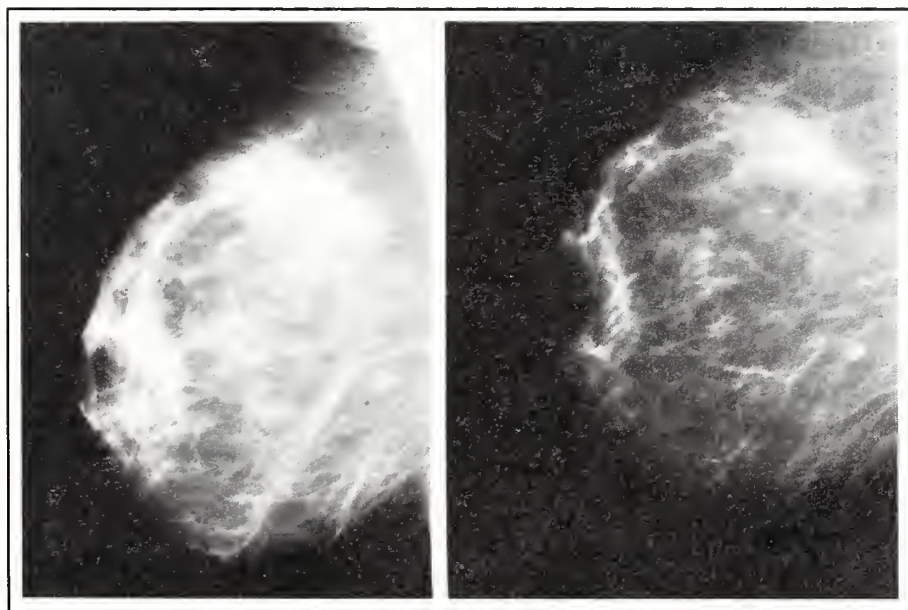


Fig. 4. Baseline (left) and 1-year follow-up (right) mammogram of subject receiving the prototype contraceptive regimen. A substantial reduction in the parenchymal densities is evident.

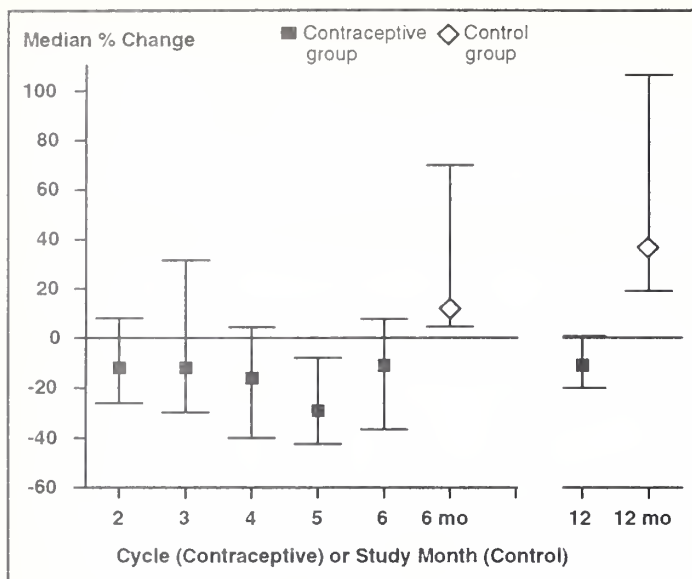


Fig. 5. Change in total symptom scores in contraceptive and control subjects. Error bars = interquartile range.

GnRHA alone for the treatment of benign gynecological disorders (8), and this too appears to be reversed when the GnRHA is stopped (69).

ERT alone or combined with a progestogen is well known to reduce BMD loss in postmenopausal women, mirrored in a much reduced fracture risk in ERT-treated women (70). A CE dose of 0.6 mg per day has been reported to eliminate bone loss in both naturally menopausal women (71) and oophorectomized women (72). The study of oophorectomized women, however, had only six subjects treated with 0.6 mg per day immediately after surgery; these women had an average loss of 0.3%, but the results in different women were widely different (standard deviation of 5.1%) (72).

In our pilot trial, despite the use of a CE dose thought to be adequate, an annualized decline of 2%-3% in lumbar spine BMD was seen (51). Clinical trials with 1.25 mg per day of esterified estrogens in surgically oophorectomized women have shown no loss of BMD following 2 years of use (73). Thus, an increase in the estrogen dose should eliminate the small continued loss seen with the prototype contraceptive; this is, however, not necessarily desirable, since it will reduce the benefit to the breast. The suppression of ovarian androgen production by the GnRHA may account for the small continued loss in BMD seen in the present study. The long-term use of GnRHA has been shown to reduce testosterone (T) levels by 65% (74). In contrast, during the perimenopausal and early natural postmenopausal periods, T levels are relatively stable (75-77). Preliminary results we have obtained with the addition of replacement of the ovarian T to the contraceptive regimen, using methyltestosterone (MT), demonstrate no further loss of BMD.

Cardiovascular Disease

Estrogen has significant effects on cardiovascular disease. While high-dose COCs appeared to produce a short-term increase in cardiovascular disease risk, COCs that use a low-dose (30-35 µg) of ethinylestradiol have little effect on cardiovas-

cular disease risk, except possibly in women at high cardiovascular disease risk (7,78).

ERT given to postmenopausal women reduces risk of cardiovascular disease (79). A major reason for the postmenopausal reduction in risk is likely to be the beneficial effects of ERT on serum cholesterol (80). High-density lipoprotein cholesterol (HDL) appears not to change with natural cessation of ovarian function, since cross-sectional epidemiologic studies show that it does not change with age over the menopausal age range, while low-density lipoprotein cholesterol (LDLC) increases significantly (81,82). The effects of GnRHAs alone on cholesterol are not as one would predict from the effects of menopause on cholesterol, since HDLC increases substantially in premenopausal women receiving a GnRHA alone (8); this probably results from the suppression of ovarian T production (51). In our pilot trial, favorable increases in HDLC were seen and were greatest in the cycles in which MPA was not administered (51). The addition of the oral MT to the regimen has eliminated the benefit of the regimen on cholesterol patterns.

Endometrium and Vaginal Bleeding

Endometrial hyperplasia is a significant clinical concern with ERT use in postmenopausal women and would be so with the prototype contraceptive regimen if a progestogen were not administered. Progestogen therapy for 12-13 days appears to be the minimum necessary to completely control ERT-induced endometrial hyperplasia and to achieve the desired histological changes in the endometrium (83,84), but there is evidence to suggest that a progestogen is not required every ERT-treatment cycle (85). A small proportion of women will develop hyperplasia if progestogens are not given every cycle, but few will develop symptoms, and a 13-day MPA course every fourth cycle will eliminate any hyperplasia that has developed (85). In our pilot trial of the prototype contraceptive, endometrial biopsies at 1 year showed no evidence of endometrial hyperplasia (51). Unscheduled bleeding or spotting occurred infrequently and declined with time on the prototype contraceptive; scheduled bleeding occurred following each period of MPA use, i.e., every 4 months (51).

The effect of the prototype contraceptive on endometrial cancer risk can be predicted, using the mathematical model previously described (1,8,16). This model accurately describes the known endometrial risk factors, including that of the increased risk from both premenopausal and postmenopausal obesity, the increased risk from use of ERT, and the decreased risk from use of COCs. Epidemiologic studies show that low-dose ERT increases risk of endometrial cancer significantly less than high-dose ERT and that the increased risk from ERT is roughly proportional to ERT dose (10). On this basis, it can be estimated that 0.625 mg per day of CE given *postmenopausally* for 24 days in each 28-day cycle for 10 years should increase the endometrial cancer rate by 170% (relative risk, 2.70), as has been observed (10). The addition of 13 days of MPA every fourth cycle may reduce this increased endometrial cancer rate to zero, but a more cautious approach suggests that the increased endometrial cancer rate will be reduced to 134% when given *postmenopausally* (10). To estimate the effect on endometrial cancer risk of the prototype contraceptive regimen, we have as-

sumed that GnRHA use will induce a medical oophorectomy and that the effect of the add-back therapy is as cautiously calculated for postmenopausal women. Compared to normal cycling *premenopausal* women, our calculations suggest that there will be a modest lifetime reduction in risk of endometrial cancer with even short-term use of the proposed regimen (8,16).

Ovary

During the period of contraceptive use, ovarian function is suppressed by the GnRHA. Recovery of menstrual function occurred on average within 90 days following 6-8 months of treatment of premenopausal women with GnRHA alone for benign gynecologic disorders (86-89). In the five women who have completed the study, the median time to recovery of ovarian function is 117 days following the last dose of luprolide acetate depot.

Protective risk factors that have been consistently found in epidemiologic studies of ovarian cancer are high parity and use of COCs (3,5,6). With increasing parity or increasing duration of COC use, ovarian cancer risk declines steadily. Although the available data are too limited to permit firm conclusions, DMPA use may not reduce ovarian cancer risk (90), possibly because follicular activity continues in women receiving DMPA. The complete suppression of ovarian function by GnRHAs should protect against ovarian cancer to the same (or greater) extent as COCs. Use for only 5 years is predicted to reduce the lifetime risk of ovarian cancer by as much as 40%; use for 15 years should reduce the risk by more than 80% (Table 2). The add-back sex steroids should have no effect on this reduced risk.

Conclusions

Studies of normal breast epithelial cell proliferation kinetics in premenopausal women show that cell proliferation peaks in the luteal phase of the menstrual cycle, consistent with a mitogenic effect of both estrogens and progestogens. Cell proliferation is not reduced in women receiving COCs, consistent with the epidemiologic evidence that COCs do not prevent breast cancer. A mitogenic effect of both estrogens and progestogens in the breast can explain epidemiologic data concerning endogenous and exogenous hormones and breast cancer risk.

The substantial evidence from studies of ERT use by postmenopausal women and the hormonal effects of current contraceptives suggest that a contraceptive with reduced levels of both estrogen and progestogen will be well tolerated and safe. To reduce the dose of sex steroids in the contraceptive, a GnRHA must be used to suppress ovarian function. The pilot trial with a prototype of such a contraceptive shows the approach is well tolerated, with some women benefiting from a reduction in premenstrual symptoms.

With current depot-release technologies, it should be possible to formulate a depot contraceptive that would require administration only three or four times per year. The contraceptive would release the GnRHA, estrogen, and testosterone over a period of 90 or 120 days; the progestogen would be released during the first 2 weeks following each administration. Menstrual bleeding would occur several weeks after each administration, i.e., only three or four times per year. The GnRHA

dose should suppress ovarian function; the dose of sex steroids must be sufficient to prevent any signs or symptoms of sex-steroid deficiency, must maintain normal BMD, and must have acceptable or beneficial effects on cholesterol. The successful development of such a contraceptive could have enormous consequences, adding substantial lifetime protection against breast cancer to the health benefits of current contraceptives.

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Estrogen-Replacement Therapy in Younger Women With Breast Cancer

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Approximately 25% of breast cancers occur in premenopausal women. In addition to local therapy, surgery or surgery plus irradiation, systemic chemotherapy administration has become the standard of care for all node-positive and many node-negative patients. Systemic adjuvant chemotherapy can result in ovarian dysfunction or failure. This renders many women prematurely estrogen deficient. The consequences of menopause, genitourinary atrophy, bone loss, and increased risk of cardiovascular disease, have not been routinely assessed in clinical trials. The risks of estrogen deficiency have not been assessed in comparison to improved disease-free and overall survival benefits of adjuvantly treated premenopausal breast cancer patients. Estrogen-replacement therapy in postmenopausal women has been shown to prevent osteoporosis and reduce fracture risk. The majority of studies also show a marked reduction in cardiovascular disease and mortality. Estrogen-replacement therapy has been considered a disease-prevention strategy rather than a therapeutic intervention. The risks and benefits of estrogen-replacement therapy in women with primary breast cancer are unknown. It is unknown how the well-known benefits accrued from reduction in skeletal and cardiovascular morbidity/mortality compare with the potential risks of increased breast cancer morbidity/mortality. Carefully designed prospective clinical trials with well-defined objectives and endpoints are required to learn if more harm than good is done by the withholding of estrogen therapy in breast cancer patients. [Monogr Natl Cancer Inst 16:149-152, 1994]

As the number of women with newly diagnosed breast cancer increases and the number of women surviving as a result of adjuvant therapy and early detection also increases, it is prudent to consider treatment-related effects exclusive of disease-free and overall survival from breast cancer. Approximately 25% of breast cancers occur in premenopausal women. As a group, they derive the greatest benefit from adjuvant chemotherapy (1). Previous consensus conferences have recommended adjuvant therapy as the standard of care for all node-positive women, as well as the consideration of adjuvant therapy for node-negative women (2,3). A significant proportion of women treated with chemotherapy become amenorrheic (4-7). Amenorrhea is related to the dose and chemotherapy agent(s) used (8). Gonadal toxicity resulting in amenorrhea is common in premenopausal women receiving adjuvant chemotherapy. Some trials indicate

ovarian failure may occur in as many as 89% of adjuvantly treated patients. Treatment-induced amenorrhea has been shown to be a function of age and duration of treatment for fluorouracil, doxorubicin, and cyclophosphamide (FAC) and cyclophosphamide, methotrexate, and fluorouracil (CMF) treatment programs (4,5). In FAC-treated patients at the M. D. Anderson Cancer Center, 96% of women greater than 40 years of age become estrogen deficient as a result of chemotherapy-induced ovarian failure (7). While the average age of menopause is reported to be 50 years, in the adjuvantly treated breast cancer population, it may be as much as 10 years earlier. The long-term life-threatening consequences of gonadal failure have not yet been demonstrated in breast cancer clinical trials. Nevertheless, an increasing number of women become at risk as more women with breast cancer are treated with systemic therapy. The non-malignancy-related consequences of adjuvant chemotherapy-induced amenorrhea have not been examined in a consistent prospective fashion.

The health consequences of menopause are well recognized. There are four areas of concern: vasomotor symptoms and neurocognitive/neuropsychiatric function; genitourinary signs and symptoms, including vaginal atrophy and dyspareunia; skeletal effects, osteoporosis, and associated bone-related morbidity; and cardiovascular effects, especially fatal cardiac events.

Vasomotor Symptoms and Neurocognitive/Neuropsychiatric Functioning

The incidence/prevalence of vasomotor symptoms, changes in neurocognitive function, and neuropsychiatric function have not been assessed as sequelae in trials of the successful treatment of primary breast cancer. In an assessment of ovarian failure consequences in an acute leukemia population, Cust et al. (9) reported menopausal symptoms or signs in 33 of 36 patients. Symptoms included vaginal dryness, hot flashes, and night sweats. The majority of patients who resumed sexual activity reported problems with sexual function. Anxiety related to concerns about sterility, femininity, and appearance were reported

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See "Note" section following "References."

for women of all ages, irrespective of marital state. Treatment with estrogen-replacement therapy was successful in some, but not all, patients (9).

Neurocognitive and neuropsychiatric function has not been evaluated in the acutely estrogen-deficient breast cancer patient population. While neurotoxic effects of specific drug therapies have been recognized, organized programs of assessment and functional intervention are lacking (10). Assessment of treatment-related effects and hormone-deficient effects independently have not been done.

Genitourinary Symptoms and Signs

There have been no long-term studies of genitourinary consequences of chemotherapy-induced amenorrhea in premenopausal breast cancer patients. To date, there is not a standardized validated menopausal symptom/sign assessment tool for use in the breast cancer population. Some quality-of-life instruments address sexual functioning, but long-term (>5 years) post-treatment quality-of-life assessment has not addressed genitourinary signs/symptoms. Atrophic vaginitis is the major physical finding that may develop within 5-10 years of menopause.

Skeletal Effects

Bone loss of 3%-5% per year occurs as a result of menopause in the non-breast-cancer population and early oophorectomy accelerates this loss (11-13). This results in clinical osteoporosis that may lead to spine, hip, and wrist fractures. As many as 50% of women over age 45 may be affected by osteoporosis. Osteoporosis is recognized as a major cause of morbidity and mortality and has been the subject of recent reviews (14-16). In addition, chemotherapy is toxic to bone cells. No data are available regarding the potential adverse effects of chemotherapy on osteoblast/osteoclast cell functioning, bone remodeling, and osteoporosis development independent of estrogen deprivation. The development of osteoporosis and osteoporosis prevention has been assessed in a trial of successfully treated Hodgkin's disease patients (17). This study demonstrated that lumbar spine and radius bone mineral density in premenopausal Hodgkin's disease patients who developed amenorrhea as a result of treatment (mean age, 36 years) was equivalent to a normal postmenopausal population (mean age, 61 years). This is consistent with accelerated osteoporosis development in young women with chemotherapy-induced ovarian failure. Estrogen-replacement therapy only partially prevented the reduction in bone density. Cross sectional and longitudinal studies of bone loss in prematurely estrogen-deficient breast cancer patients are needed.

Cardiovascular Effects

Cardiovascular disease remains the leading cause of death for women in the United States. In non-breast-cancer population women, the risk of cardiac disease increases dramatically after menopause and is directly related to estrogen deficiency. Long-term cardiovascular risk assessment and lipid assessment have not been a component of adjuvant clinical trials in breast cancer.

Cardiovascular disease accounts for twice as many deaths in women (more than two-thirds of all deaths) as cancer (16). Competing causes of death in long-term survivors of breast cancer have not been subjected to the same rigorous analyses as have the improvement in disease-free and overall survival from adjuvant therapy for breast cancer. In this regard, cancer has always been assumed to be the worse thing that can happen.

Estrogen deficiency resulting from drug-induced premature ovarian failure has the potential to cause great harm. Menopausal women without hormone-replacement therapy have a significantly higher all-cause mortality, but especially mortality from coronary heart disease (18-20). Reduction in mortality for estrogen users has been shown in women with prior hysterectomy and oophorectomy, as well as in those with no prior gynecologic surgery (21).

Estrogen Risk

In women with a history of primary breast cancer, the concern with estrogen-replacement therapy is the potential for added morbidity and mortality from activation or growth acceleration of breast cancer micrometastases or the development of a second primary breast cancer. The role of estrogen receptors and estrogen-dependent growth factors in the regulation of breast cancer proliferation continues to unfold in many laboratories. In cell and rodent model systems, estrogens may act to promote growth and progression of tumor through effects on cell proliferation. They may act as permissive agents for transformation by carcinogens of mammary cells to the malignant phenotype. Estrogen has not been shown to be a carcinogen. While the laboratory evidence convincingly presents estrogen as a contributor to breast cancer development, the observational data regarding the risk of developing breast cancer for women treated with estrogen are less convincing. Case-control, cohort, and prospective studies have not resolved whether estrogen replacement increases the risk of breast cancer development in all women, some women, or no women (21). Meta-analyses have not resolved this issue (22-24). While opinions on either side of this controversy have been expressed, there are no prospective studies of the risk of second primary breast cancer in women treated with estrogen-replacement therapy after a first breast malignancy.

Endometrial cancer development is increased for women who receive estrogen-replacement therapy (25). Unopposed prolonged estrogen use has been reported to increase the risk of endometrial cancer up to 15-fold (26,27). Estrogen-associated endometrial cancer usually has an excellent prognosis due to early-stage detection and favorable histologic features. Estrogen-treated women with endometrial cancer may have a better overall survival than those without cancer not treated with estrogens (28). A recent review concludes that there are insufficient data to calculate a relative risk for estrogen users dying from endometrial cancer (27).

Pregnancy after a diagnosis of primary breast cancer is associated with profound hormonal changes. These changes do not seem to have a deleterious effect on disease recurrence, metastasis, development, or overall survival. This appears to be true irrespective of disease stage or axillary nodes status (29).

While additive hormonal therapy for metastatic breast cancer has largely been supplanted by use of the estrogen antagonist/agonist tamoxifen, tumor responses to estrogen have been well documented in the postmenopausal breast cancer population (30). Interestingly, there are some data that suggest that postmenopausal women receiving estrogen-replacement therapy prior to the diagnosis of primary breast cancer have a more favorable prognosis than their nonestrogen-exposed counterparts (31,32).

The proscription for estrogen administration in women with a history of primary breast cancer is not based on clinical trial results. Concern for breast cancer recurrence is heightened for estrogen-receptor positive tumors, a minority in premenopausal women, and for those in whom the statistical probability of micrometastatic disease is high, multiple positive axillary lymph nodes. As physicians, especially physicians who experience with their patients the consequences of metastatic disease, we are loathe to contribute to the risk of metastases development.

Estrogen Benefits

Estrogen-replacement therapy is the only effective therapy for vasomotor symptoms and genitourinary atrophy that accompany menopause (33,34).

Mass screening of women for bone loss and fracture risk assessment has not been recommended. Screening has been recommended for women at increased risk of osteoporosis development and as a measure of therapeutic efficacy for those placed on estrogen-replacement therapy (35).

Fracture risk for hip and vertebral fractures has been shown to be related to bone-mineral density and age; fracture risk increases with decreasing bone-mineral density as well as increasing age (36,37). In the development of a model to assess the lifetime impact of osteoporosis, it was estimated that 54% of 50-year-old women would develop an osteoporotic fracture during their remaining life span (38).

Skeletal benefits of estrogen, manifested as reduced fracture incidence and risk as a result of osteoporosis prevention, have been seen in many clinical trials. The prophylaxis and treatment of osteoporosis have been reviewed by many who have concluded that estrogen can prevent osteoporosis by reducing bone loss at all skeletal sites (15-17,21). This leads to a reduction in hip and vertebral fractures and the attendant morbidity/mortality of these fractures (39). Estrogen has been shown to prevent spinal bone loss and in a decision analytic model and estrogen replacement has been reported to be "virtually without risk" when cardiovascular effects are also considered (40,41).

Cardiovascular disease benefits have been shown in prospective, case-control, and population-based studies (27,34). Most studies show an approximate 50% reduction in cardiac events, including sudden death and acute myocardial infarction. Estrogen induces favorable changes in serum lipids, including reductions in low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol (42,43). It is not clear if the favorable cardiovascular effects of estrogen-replacement are mediated entirely by changes in lipids, the vasculature, or by some as yet unknown factor(s) (44,45).

A recent review of hormone therapy as a disease-prevention strategy suggests that women at increased risk of breast cancer development treated with hormone-replacement therapy can expect an increase in life expectancy due to a reduction in mortality from coronary heart disease and hip fracture (25). This is consistent with the finding of Bush et al. (21) who reported relative risks of mortality for estrogen-replacement therapy of 0.54 in women without hysterectomy and 0.34 in women with hysterectomy.

Henderson et al. (20) reported a reduction in all cause mortality (20%), including not only reductions in atherosclerotic vascular disease-related death but also reduced mortality from cancer.

At present, we are operating from the perspective of a black box vis-à-vis estrogen-replacement therapy and breast cancer risk in women with primary breast cancer. Analogous to the situation with endometrial cancer, estrogen use for disease prevention in menopausal women is proscribed. However, in the endometrial cancer patient the sentiment is changing as results of clinical trials begin to show no increase risk of cancer recurrence or mortality for replacement hormone use (46).

In the prematurely estrogen-deficient younger women with breast cancer, there are competing health risks—breast cancer morbidity/mortality versus cardiovascular/skeletal morbidity/mortality. Younger women have the greatest potential longevity as a result of adjuvant chemotherapy and the greatest potential risk for cardiovascular and skeletal morbid events. The balance of these risks is unknown.

Well-designed clinical trials assessing genitourinary, skeletal, and cardiovascular risk are lacking. Long-term risk assessment in premenopausal women who become amenorrheic has been limited primarily to the cancer-related questions, disease-free and overall survival, and acute drug-related toxic effects. A brief report of combination estrogen/progestogen hormone-replacement therapy suggests no increase in cancer recurrence at a 2-year follow-up. Women were treated for a limited time period of 3 months. Patient characteristics and eligibility for treatment and response criteria were not presented (47).

The potential benefits of bone-disease prevention, cardiovascular disease prevention, and reduction in all-cause mortality have not been assessed for estrogen administration in women with a history of breast cancer (48,49).

What is known, and more importantly what is unknown, about hormone-replacement therapy requires thoughtful, well-conceived, well-conducted clinical trials to resolve the conflict of benefit/risk for hormone-replacement therapy in premenopausal women with a history of primary breast cancer.

Issues of appropriate biological questions, patient eligibility, analysis determinants for risk/benefit, and appropriate hormone intervention have not been defined.

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Randomized Prospective Trial of Estrogen-Replacement Therapy in Women With a History of Breast Cancer

*Rena Vassilopoulou-Sellin, Richard L. Theriault**

With the onset of menopause, women develop increased risk for heart disease, vasomotor instability, and osteoporosis, which is related to estrogen deficiency, and can be corrected with estrogen-replacement therapy (ERT). Menopausal women with a history of breast cancer are advised against estrogen therapy because of concerns that ERT may adversely affect the course of the disease. There have been no prospective studies that address the issue of risk versus benefit for ERT in women with a history of breast cancer. We have initiated a randomized, prospective clinical study to define the influence, if any, of ERT on the clinical course of breast cancer (measure of potential risk) and the efficacy of ERT in the treatment of metabolic bone derangements (measure of benefit). Changes in serum lipids, cardiovascular events, and indices of psychological well-being are compared but do not constitute statistical end points. Eligible women must have had stage I or stage II breast cancer and must have had no evidence of disease for at least 2 years since therapy if estrogen-receptor-negative disease or for at least 10 years if the estrogen-receptor status is unknown. They were randomized to receive ERT (Premarin at 0.625 mg, days 1-25) versus no intervention (study control). Parameters of benefit and risk will be measured to detect a 10% change in disease-free rate for up to 5 years, with interim analyses at 20, 30, and 36 months of patient accrual. This study will allow us to begin the development of safe and effective strategies for the management of estrogen deficiency in patients with breast cancer. If the safety of ERT can be established in this narrowly selected group, further clinical studies can be designed to define the potential role of ERT in other subgroups of women with this disease. [Monogr Natl Cancer Inst 16:153-159, 1994]

With the onset of estrogen deficiency, women develop increased risk for heart disease, vasomotor instability, and metabolic bone disease. The benefit of estrogen-replacement therapy (ERT) in reducing the risk from these complications is well established; ERT is considered the standard of care for most postmenopausal women in the general population. Women who have had breast cancer also develop estrogen deficiency due to natural menopause or, prematurely, due to antineoplastic chemotherapy. However, women with breast cancer are advised against estrogen therapy because of concerns that ERT may ad-

versely affect the course of breast cancer. There have been no controlled prospective studies that address the issue of risk versus benefit for ERT in women with a background of breast cancer.

Population at Risk

It is estimated that more than 180 000 women per year will be treated for newly diagnosed breast cancer. The majority of these women will be menopausal. Many premenopausal patients who will receive adjuvant chemotherapy will also become menopausal. While there remains a debate as to whether it is advisable to administer chemotherapy to node-negative patients, studies showing improved disease-free survival in these patients contribute to the opinion that chemotherapy represents an important therapeutic option (1). In practice, more and younger patients are being treated with adjuvant chemotherapy.

As survival and disease-free survival of these adjuvantly treated patients improve, the consequences of therapy need to be assessed. Ovarian dysfunction is a common complication of treatment with cytotoxic agents. Ovarian function has been shown to be affected by chemotherapy in a variety of clinical circumstances, including neoplastic and non-neoplastic disease states (2-4). Amenorrhea and ovarian dysfunction with single and multiagent adjuvant chemotherapy in premenopausal breast cancer patients have been age-dependent in a number of studies (5-8).

Viewed from the public health care perspective, the number of women with near-normal life expectancy, who reach menopause after the diagnosis of localized breast cancer, is ever increasing due to early diagnosis and improved therapy. At this time, of 65 million women from the United States under the age of 50 years, one of 50 is likely to have breast cancer; of these, approximately 50% have had localized disease and carry a 90% 5-year survival rate. Approximately two thirds of premenopausal women have estrogen-receptor (ER)-negative tumors. Thus, more than 500 000 women will reach menopause at the

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See "Notes" section following "References."

age of 50 years, having survived for at least 5 years after the diagnosis of localized breast cancer. In addition, of approximately 180 000 new cases of breast cancer each year, 23% are in women younger than 50 years; localized disease and good survival expectations are also true for 50% of patients in this group as well. Thus, almost 20 000 additional women each year are added to the population who will reach menopause at the age of 50 years, with excellent prognosis after the diagnosis of localized breast cancer. These women face several decades of estrogen deficiency because of current medical opinion that estrogen is contraindicated for the management of menopause in women who have had breast cancer. There are no prospective studies to support this medical practice.

Postmenopausal Estrogen Replacement: Breast Cancer Risks

The association between breast cancer development and the use of hormonal agents has been the subject of controversy and conflicting literature reports. For premenopausal women, most studies of oral contraceptive hormone use indicate no increased breast cancer risk, while reports of either increased or decreased risk are also available (9-14). In postmenopausal women, ERT has been shown to confer a small increase in relative risk for the development of breast cancer (related to the dose and duration of estrogen administration) in some but not other studies (15-25).

ERT in Women With a History of Breast Cancer

Whether or not the use of supplemental low-dose ERT has any impact on recurrence or longevity in postmenopausal women who have had breast cancer is entirely unknown. In experiments of nature, women who become pregnant after the diagnosis and treatment of breast cancer (surgery, radiotherapy, adjuvant chemotherapy, and combinations thereof) do not appear to have increased risk of recurrence or death from breast cancer (26-28). Finally, women who develop breast cancer while receiving ERT may have improved outcome relative to nonusers of ERT (29). Overall, the concern that estrogen administration (especially in physiological replacement doses) promotes the growth of breast cancer in humans, remains unsubstantiated. In a recent special topic conference regarding ERT, it was concluded that the association between postmenopausal ERT and increased risk of breast cancer has not been proven and that previous breast cancer should only be considered a relative contraindication to the prescription of otherwise indicated estrogen replacement (30).

No previous controlled, prospective studies are available that address the risks versus benefits of ERT in this group of women. Because ERT confers significant benefits in terms of quality of life, reduction in cardiovascular morbidity/mortality, and reduction in the morbidity/mortality associated with osteoporosis and because of the lack of any available data regarding estrogen use in this setting, we have established a prospective, randomized trial of ERT for postmenopausal women with a background of localized breast cancer.

ERT in Women With Breast Cancer: Survey of Patient Attitudes at M. D. Anderson Cancer Center

Very little is known about the attitudes of women in the general population concerning ERT; there are no data analyzing the views of women with breast cancer about this vexing issue. Clearly, the attitude of such women regarding ERT is critical in the design of appropriate strategies for the management of their menopause. A randomly selected group of 224 women with breast cancer responded to an anonymous survey (31) addressing the following: the presence of menopause, antecedent therapies, symptoms related to estrogen deficiency, concerns about osteoporosis or heart disease, and attitude about ERT and perception about ERT-related cancer risk.

Among women who completed the survey, 77% were menopausal and 81% had multimodality therapy. Of menopausal women, 27% felt that they needed some treatment for menopause, and 8% had taken ERT since cancer diagnosis. Most women were afraid that ERT may precipitate cancer recurrence (78%) but were concerned about menopause-related risk of osteoporosis (70%) and heart disease (72%) (Table 1). Overall, 44% of menopausal women were willing to consider ERT under medical supervision; those treated with surgery alone were distinct in that 71% would consider ERT ($P<.04$) (Table 2). Among premenopausal women, 59% expressed interest in eventual ERT. Premenopausal women were more concerned about osteoporosis (82% versus 66% for postmenopausal) and heart disease (92% versus 73%) and that ERT may precipitate cancer recurrence (98% versus 73%) but were, at the same time, more

Table 1. Impact of menopause on patient concerns*

	Menopausal	Premenopausal
Osteoporosis		
Very	34/154 (22)	10/45 (22)
Some	68/154 (44)	27/45 (60)
Not	52/154 (34)	8/45 (18)
Cardiovascular		
Very	42/157 (27)	15/47 (32)
Some	72/157 (46)	28/47 (60)
Not	43/157 (27)†	4/47 (9)†
Fear recurrence		
Very	64/149 (43)	15/43 (35)
Some	44/149 (30)	27/43 (63)
Not	41/149 (27)†	2/43 (2)†
Consider ERT	54/135 (40)	23/39 (59)

*Values = No. of responders/No. answering question (% of patients).

† $P<.05$ for menopausal versus premenopausal.

Table 2. Attitude of 127 menopausal women regarding ERT (impact of prior therapy)

Therapy	Consider ERT	No interest
Surgery	10/14 (71%)	4/14 (29%)
All other*	41/113 (36%)	72/113 (64%)

*Chemotherapy, radiotherapy, and surgery in all combinations. No difference between chemotherapy vs. tamoxifen.

willing to consider ERT under medical supervision (59% versus 40% for menopausal).

This study underscores the fact that women with breast cancer are very aware and concerned about the adverse health consequences of estrogen deficiency. While they are afraid about the possibility that ERT may precipitate cancer recurrence, they are interested in exploring the possibility of ERT under medical supervision. Despite the prevailing opinion that ERT should be avoided in this setting, a small number of patients opt for ERT outside the setting of oncologic supervision, presumably because of debilitating menopausal symptoms. The survey results suggest that treatment background, menopausal status, and symptomology affect patient attitudes toward ERT.

Estrogen Replacement in Women With Breast Cancer: A Survey of Physician Attitudes

A one-page questionnaire inquiring into current practices and prevailing attitudes regarding ERT after the diagnosis of breast cancer was mailed to 2170 physicians practicing in Harris County, Tex. (family practice, internal medicine, cardiology, general surgery, gynecology, and orthopedics). We received 152 (7%) replies (Table 3). Overall, only 32% of practitioners stated that they were aware of patients with prior breast cancer who take estrogen at present; these patients appear to represent a small minority in their practices. We were interested to find out that only 29% of physicians were of the personal opinion that ERT is related to breast cancer recurrence.

There were 50 physicians who specified that they prescribe ERT and who outlined their approach (Premarin versus cream, etc.). Among these, 82% stated that they care for patients with prior breast cancer who take ERT at present. While 54% of the physicians stated that tumor ER status was important in their considerations, the other 38% did not consider this aspect of his-

tory important. Furthermore, only 12% of these physicians felt that ERT may be related to cancer recurrence (Table 4).

This survey confirms the findings of our earlier patient survey that there are small but significant numbers of women on ERT after the diagnosis of breast cancer; ERT is prescribed in a fragmented fashion that does not lend itself to scientific scrutiny regarding safety. The comments point out that most physicians avoid ERT in such women not because they, personally, believe it to be harmful but because the lack of definitive data and guidelines makes the prescription of ERT medically and legally hazardous. Both surveys underscore the importance of deriving objective information as to whether and for which subgroups ERT represents safe treatment of menopausal sequelae after the diagnosis of breast cancer.

Study Design and Methods

Eligibility Criteria for Participation in a Prospective, Randomized Study

There are no clinical guidelines regarding ERT in postmenopausal women with prior diagnosis of breast cancer. The present study has been initiated so that specific criteria of benefit versus risk can be gradually developed for this growing population of women. Our intention has been to select a group of women who anticipate a relatively long, disease-free lifespan after the onset of menopause and who have least theoretical risk from reintroduction of estrogen. Thus, we may expect to optimize the potential benefit of ERT while minimizing the potential risks.

We have chosen to include the following two subgroups: 1) women with stage I or stage II ER-negative breast cancer, who have no evidence of disease for at least 2 years after initial therapy, as determined by the evaluation of their primary care oncology team, and 2) women with stage I or stage II tumors with unknown ER status who have had no evidence of disease for at least 10 years. Our rationale has been that ER status information is often unavailable in patients with distant disease; such

Table 3. Prevailing attitudes regarding ERT in women with history of breast cancer among physicians practicing in Harris county, Tex*

Are there patients with history of breast cancer in your practice?	
None	10
<10 y	64
10-30 y	44
>30 y	28
No answer	6
Are there patients with history of breast cancer on ERT in your practice?	
None	89
<10 y	46 (32)
10-30 y	1
>30 y	2
No answer	4
Has ER status of tumor been a factor in prescribing ERT since diagnosis of breast cancer?	
Yes	64
No	51
No answer	36
Have you had the impression that ERT has been related to breast tumor recurrence?	
Yes	42 (29)
No	78
"Depends"	9
No answer	23

*Values = No. of responders (%).

Table 4. Prevailing attitudes regarding ERT in women with breast cancer among 50 physicians who prescribe estrogen in their practice*

Are there patients with history of breast cancer in your practice?	
<10 y	15
10-30 y	20
>30 y	15
Are there patients with history of breast cancer on ERT in your practice?	
0	6
<10 y	41 (82)
10-30 y	1
>30 y	2
Has estrogen receptor status of tumor been a factor in prescribing ERT since diagnosis of breast cancer?	
Yes	27 (54)
No	19 (38)
No answer	4
Have you had the impression that ERT has been related to breast tumor recurrence?	
Yes	6 (12)
No	39
No answer	5

*Values = No. of responders (%).

patients may represent a group that has oncologically low risk for recurrence but metabolically high risk for postmenopausal problems.

Because the natural history of carcinoma in situ is different from that of invasive breast cancer, patients with this early lesion are not included in the present study. Because the biology of breast cancer/estrogen interactions is thought to depend on the presence of estrogen receptors, no patients with documented ER(+) tumors are included.

Human Subject Considerations

In response to the Women's Health Initiative, the present clinical study focus pertains to health maintenance issues particularly relevant to older women. Both breast cancer and menopause are conditions that overwhelmingly affect women. Breast cancer in men is very rare, and men do not develop menopause; thus, the present study does not include men. The study is designed to include healthy women who have developed menopause after the diagnosis of breast cancer; they must be free of disease without cardiovascular disease at the time of enrollment. Informed consent will be obtained. They will be randomized to receive either estrogen replacement (standard of care for most postmenopausal women without breast cancer) or no estrogen (current standard of care for postmenopausal women who have had breast cancer). In the absence of any direct data that ERT is, in fact, contraindicated after breast cancer, the present study is specifically designed to define safety guidelines for ERT after the diagnosis of breast cancer (thus making certain that these women are not, unnecessarily, being denied efficacious and safe therapy for menopause-related symptoms and diseases). Potential hazard consists of the possibility that ERT may, in fact, prove to adversely affect cancer recurrence; this is central to the study design. Statistical considerations have been weighed towards early detection of potential ERT risk. Therefore, and because women with localized breast cancer who have been rendered disease free after primary therapy have low recurrence risk, we have set a slow accrual rate of four new participants per month. We, thus, hope to minimize the possibility that ERT risk will be undetected for a prolonged period of time or that many women will have been placed at risk before we can detect such potential hazards.

The existence and purpose of the study will be presented to potential participants during the course of their oncologic follow-up visits and/or through circulation of descriptive information in medical publications and newsletters. It has been our experience, so far, that most study participants have asked their physicians about possible estrogen therapy and have been referred to us because of increasing awareness that our program exists. All participants will receive thorough explanation of study design and will be asked to review and to sign informed consent (as required and approved by the Institutional Review Board of the M. D. Anderson Cancer Center).

Choice of Hormone-Replacement Regimen

Conjugated estrogens have been used in most North American studies and appear to provide a lower relative risk for the subsequent development of breast cancer than other syn-

thetic estrogen formulations. The beneficial effect of ERT on cardiovascular morbidity and mortality has been established in studies, using the oral route of estrogen administration. Prevention of osteoporosis has been demonstrated with moderate, rather than "lowest" estrogen doses. Therefore, we plan to use oral Premarin at a dose of 0.625 mg on days 1-25 each month; dose may be increased to 1.25 mg if serum follicle-stimulating hormone (FSH) does not diminish with initial dose.

The addition of cyclical progesterone to an ERT regimen decreases the increased relative risk of endometrial cancer associated with administration of unopposed estrogens for long periods of time. However, progesterone may have independent, opposite effects on serum lipids and on the risk for subsequent breast cancer. In breast cancer, progesterone receptors on the tumor are emerging as important biological determinants of disease outcome and response to therapy. Concerns about the safety of ERT even in ER(-) tumors are prompting the present study; for progesterone, we know nothing about the potential impact of progesterone administration and are even less able to control for ER(-) tumor status. Thus, for the purposes of the present study, we have chosen to avoid progesterone administration so that we can assess the impact of only one hormonal parameter (i.e., estrogen).

Tamoxifen is under investigation for its potential estrogenic benefits on serum lipids and bone mineral density; long-term potential reduction of cardiovascular mortality and bone fracture risk has yet to be demonstrated. In addition, climacteric vasomotor symptoms tend to deteriorate, and additional toxic effects exist for this compound. The potential for combined estrogen and tamoxifen programs in the long-term management of menopause for women who have completed treatment for breast cancer remains to be clarified. We have chosen to omit a combination regimen now so that we can clarify the safety profile of conjugated estrogen alone.

Study Design

Eligible women will be randomly assigned to receive either no treatment or Premarin of 0.625 mg orally on days 1-25 of each month for the duration of their participation in the study (limit, 5 years). Randomization is based on age at diagnosis and ER status; it is performed by computer after consent is signed and is supervised by the M. D. Anderson Cancer Center patient data management system (PDMS); all information is stored and monitored through this program. Follow-up is done at The University of Texas M. D. Anderson Cancer Center at 3- or 6-month intervals. The primary care physicians of all participants are informed of the study and their consent and cooperation sought.

Pretreatment Evaluation

After the study is thoroughly explained to potential participants and informed consent is obtained, complete history and physical examination are done. Particular attention is placed on risk factors for osteoporosis and cardiovascular disease. Information is obtained regarding family history for heart disease, metabolic bone disease, personal habits that may impact on heart and bone disease (e.g., diet, exercise, tobacco), and assessment of vasomotor/genitourinary symptoms. Flowsheets are

generated to permit regular monitoring of relevant parameters during the study. Quality-of-life issues are addressed through standardized questionnaires. Laboratory evaluation includes serum lipid profile (total cholesterol low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides), serum gonadotropin FSH levels, and electrocardiogram (EKG). Baseline Pap smear and bone mineral density determinations are done.

Evaluation During Study

Patients are seen every 3 months for the first 2 years and then every 6 months for 3 years, for a total of up to 5 years. The following will be assessed during each visit: (a) history and physical examination, (b) review of tumor status, (c) measurement of gonadotropin/estrogen and lipid levels, (d) review of the potential occurrence of angina, acute myocardial infarction, or thromboembolic events, and (e) review of the potential occurrence of dysfunctional uterine bleeding. Patients who may develop dysfunctional uterine bleeding will be referred for appropriate gynecologic consultation and endometrial sampling.

Determination of disease status is under the supervision of the participants' primary care oncologist, radiotherapist, or surgeon and will be reviewed and verified during each visit. For patients with stage I and stage II disease, oncologic evaluation generally includes (a) history, physical examination, mammogram, and serum complete blood cell count (CBC)/SMA/carcinoembryonic antigen (CEA) during each visit, (b) chest radiograph during the first 2 years, and (c) bone scan during the first 5 years. In addition, the following questionnaires will be used to assess psychological issues: the General Health Questionnaire, the State-Trait Anxiety Inventory, the Beck Depression Inventory, and the M. D. Anderson Neurotoxicity Rating Scale. These tools are well standardized and often used in biomedical studies; they are brief and self-administered and assess the areas of function of interest in this protocol. Every 12 months, the following are assessed: (a) bone mineral density measurements and (b) Pap-smear surveillance.

At the time of enrollment, all participants receive information and counseling on health maintenance principles of diet, exercise, and personal habits. Attention of nonhormonal interventions is provided to the women in the control arm. Participation in the study will be discontinued for recurrence of breast cancer, protocol noncompliance, and/or evidence of estrogen toxicity.

Statistical Considerations

Statistical considerations have been weighed toward early detection of potential ERT risk. While the anticipated positive benefits of the study are given primary importance, it is essential to emphasize that early detection of potential ERT risk is pivotal in designing both accrual rates and interim analyses.

Measure of Benefit

The major comparisons for short-term benefit of ERT will be changes of lumbar spine and femoral head bone mineral density (BMD, g/cm²) at entry and at 5 years (positive endpoint). The percent changes in this measurement will be computed for each patient and the mean percent changes for the ERT and control

groups will be compared. Entry of 160 cases randomized equally to ERT or control groups will allow detection of 15% differences in bone disease. Comparison will be by *t* tests, and for each outcome measure, it is assumed that the variability in the percent changes is the same in both groups and that the standard deviation of the unit being tested does not exceed the difference to be detected. Since the variability in these changes cannot be predicted with certainty, the assumptions will be verified during the study. Testing will be at a two-sided significance level of 0.05 (allowing for a favorable change in bone density in either the ERT or control group) and power of the tests will exceed 80%. Analyses will be stratified by disease stage.

At a BMD of 0.80-0.89 g/cm², the femoral fracture incidence in women over 35 years of age is reported to be 1.4/1000 person years for intertrochanteric and 2.9/1000 person years for cervical. The incidence rises to 16.6 and 8.3 for BMD less than 0.60 g/cm² and drops to 0.4 and 1.2 for BMD greater than 0.90 g/cm². Maintenance of BMD greater than 0.89 g/cm² at 5 years will be considered a positive endpoint for ERT replacement. The postmenopausal bone loss is 2.5% per year; therefore, 5 years after enrollment in the study, ERT-treated patients are expected to have a 10%-25% greater BMD than controls.

Measure of Risk

The study is designed to detect a decrease in the 1-year disease-free rate from an expected 90% [exponential distribution ($\lambda = .0088$)] in the control group to 80% ($\lambda = .0186$) in the ERT group (an increase in risk of recurrence of $2.11 \times$ controls). At an expected accrual rate of four patients per month and an accrual phase of 40 months, the study will have 90% power to detect the designated difference in disease-free rate, with a significance level of 0.10 (one-sided); that is, there will be a 10% probability of falsely declaring a difference between the two groups or of failing to detect as statistically significant a true difference of the specified size. The type I error rate was set at 0.10 (instead of the usual 0.05) because the consequences of falsely declaring a difference in disease-free interval between the two groups were regarded as of lesser importance. Only the hypothesis of increased risk of recurrence associated with ERT will be considered.

Interim testing will be carried out so that the study may be terminated early if there is evidence of increased recurrence rate in the ERT group. The Pocock method (32) was used to provide interim testing guidelines; this method increases the likelihood of stopping the trial if there is early evidence of a difference in disease-recurrence rates, compared with other interim testing methods. Comparisons of disease-free survival will be by log-rank test, with the final analysis to be carried out 18 months following end of accrual phase. Interim analyses will be performed after approximately 24, 36, and 48 months from start of patient accrual. Tests will be carried out at nominal significance levels of 0.050, 0.042, and 0.038, respectively, with final test at significance level of 0.035. While the third test would not reduce total number of patients enrolled in the study, it would allow ERT to be discontinued among those patients already assigned to the treatment arm in the event of an adverse finding.

Other Measurements

Data from quality-of-life questionnaires, serum lipids, and cardiovascular events will be analyzed and compared for the two study groups at the end of the study; potential statistically valid interpretations will be sought. However, statistical endpoints are not included for these factors because they are difficult to incorporate into statistical calculations for the entire study population. Similarly, information derived from evaluation of nonrandomized, off-study ERT recipients will be recorded and assessed but will not be included in statistical analyses at this point.

Background Drug Information

Premarin is a commercially available preparation that is widely used in patients who require ERT, regardless of the specific pathogenesis of estrogen deficiency. Premarin (conjugated estrogen tablets USP) for oral administration contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material deprived from pregnant mares' urine. Premarin provides near-physiologic estrogen replacement in women who have estrogen deficiency. Premarin is approved for treatment of (a) osteoporosis, (b) hypoenestrogenism due to hypogonadism, castration, or primary ovarian failure, (c) vasomotor symptoms associated with primary ovarian failure, and (d) atrophic vaginitis or urethritis.

Randomized, Prospective Study of ERT in Women With a History of Breast Cancer: Preliminary Data

Active participant enrollment began in July 1992, and optimal accrual rate was set at four new participants per month for reasons of statistical considerations. As of December 15, 1992, 24 women have enrolled in the study (Table 5). Some of the women have been approached by us or their physicians; however, most have approached their physicians with estrogen deficiency problems, and their physicians have referred them to us in response. While most women have, at some point, been treated at M. D. Anderson, a few have registered at our institution solely for the purpose of joining the study. In addition to Texas, participants currently reside in Alabama, Louisiana, Mississippi, Nevada, New Mexico, and Washington, D.C.

Randomization is related to age at diagnosis and to tumor ER status (negative versus unknown). As of December 15, 1992, 12 women have been randomized to Premarin and 12 to no treatment. The two groups are, so far, comparable regarding age (median, 46 versus 45 years) and tumor ER status (negative 6 versus 7 and unknown 6 versus 5). There are no statistical differences in the baseline lipid levels, serum FSH, and bone mineral density (at the vertebral spine, right femoral neck, or left femoral neck). Incidentally, despite the recent public health emphasis on osteoporosis and heart disease prevention, the personal motive that made most women seek out the program has been climacteric symptoms. Baseline psychological testing has

Table 5. ERT in women with background of breast cancer: preliminary data of prospective study (as of 12/15/92)

	Randomized study		Off study group, (+) ERT
	(+) ERT	(-) ERT	
No. of patients	12	12	16
Median age in y (range)	46 (40-60)	45 (36-54)	47 (29-68)
Tumor, F/U§			
ER(-), <10 y	6	7	7*
ER(?), >10 y	6	5	5*
Motive			
Dyspareunia	8	4	4
Flashes	5	6	6
Depression	4	1	3
Heart risk	1	—	1
Osteoporosis	—	1	3
Lipids†			
Cholesterol (mg/100 mL)	232 ± 10	219 ± 10	226 ± 8
HDL	61 ± 4	60 ± 6	56 ± 5
LDL	146 ± 9	130 ± 9	140 ± 11
Triglycerides	143 ± 22	169 ± 26	184 ± 33
Hormones†			
FSH (mIU/mL)	82 ± 8	107 ± 10	78 ± 11
Bone mineral density†‡			
Vertebral spine	95 ± 4	90 ± 8	94 ± 4
(R) fem neck	97 ± 5	91 ± 4	88 ± 4
(L) fem neck	95 ± 5	88 ± 3	90 ± 3

*In off study patients the interval since diagnosis is quite variable; the remaining 4 patients had ER(+) tumors.

†Values = mean ± SEM.

‡Bone mineral density in g/cm² is expressed as percentage relative to sex- and age-matched normal controls.

§Tumor = tumor ER status; F/U = duration of follow-up since cancer diagnosis.

been administered to all participants, but evaluations are not yet complete.

We are also following postmenopausal women who began ERT after discussions with their personal physicians and for specific clinical indications, totally unrelated to our study. We are, at this time, monitoring 16 such patients; their disease stage, ER tumor status, and interval since therapy are obviously much more variable than of study participants. We expect that insights derived from observations of this group will provide better and broader appreciation of the overall scope of the management of menopause in women with history of breast cancer.

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Nonhormonal Alternatives for the Management of Early Menopause in Younger Women With Breast Cancer

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Current medical practice recommends the use of alternatives to estrogen-replacement therapy for the treatment of menopausal sequelae in younger women with breast cancer, although this clinical recommendation is undergoing reappraisal. Until prospective randomized studies addressing hormone use in this population are available, estrogen use in breast cancer patients will remain controversial. Because estrogen-replacement therapy is not the standard of practice and there is limited information available on nonestrogen therapies, women with breast cancer who are menopausal may not be prescribed or counseled about nonestrogen options. The efficacy, safety, and extent of use of most nonestrogen treatment modalities (other hormonal preparations, nonhormonal drugs, homeopathic preparations, and non-drug treatments) are not well documented and, unlike estrogen, many are selective in their benefit and do not share estrogen's universal impact. The use of several nonestrogen approaches for the prevention and treatment of osteoporosis has been promising. Traditional recommendations to maintain skeletal integrity, such as weight-bearing exercise; a diet rich in calcium and limited in caffeine, alcohol, and protein; avoidance of smoking; and measures to minimize trauma have been expanded to include the use or investigation of drugs (either alone or in combination). These drugs include progestins, vitamin D metabolites, injectable and intranasal synthetic salmon calcitonin, bisphosphonates, sodium fluoride, parathyroid hormone, growth factors, tamoxifen, etc. Strict control of the known risk factors, such as smoking, dyslipidemia, and hypertension as well as exercise, weight control, and the use of tamoxifen, are employed for the prevention and treatment of cardiovascular complications. A combination-prescription drug composed of phenobarbital, belladonna, and ergotamine tartrate is a frequently used nonestrogen alternative for the treatment of hot flushes as well as other vasomotor symptoms, such as restlessness and insomnia. Other drug regimens for the control of vasomotor symptoms include sedatives and tranquilizers, nonsteroidal, anti-inflammatory drugs, α -adrenergics, antidopaminergics, etc. Alternatives to traditional therapies, such as vitamins, plants (herbs, bulbs, and roots), biofeedback, stress management, modification of environment, nutritional supplements, and exercise prescriptions have sporadically been used for the treatment of menopausal problems. Although these approaches are commonly sought

by women who seek natural remedies, scant prospective data exist regarding their risks and benefits. One concern is that the active ingredient of many herbal remedies is not known; cases of toxic effects have been reported from medicinal-herbal ingestion. Younger women with breast cancer should be counseled, preferably before chemotherapy and the abrupt onset of menopause, about short- and long-term problems associated with estrogen loss and offered nonestrogen options, especially in the immediate period after the diagnosis of breast malignancy. Estrogen replacement use in breast cancer patients will be more clearly defined as data from research examining this issue become available. [Monogr Natl Cancer Inst 16:161-167, 1994]

Most women have a transition period of several years from ovarian function capable of reproduction to ovarian failure, therefore adjustment to the declining ovarian hormone levels that occur with menopause are not abrupt. Women treated for breast cancer, like surgically menopausal women, often become menopausal over a few weeks to months. The loss of estrogen may cause distressing symptoms (hot flushes, night sweats, insomnia, mood changes, etc.) that impact on quality of life and can negatively affect bone, cardiovascular, and urogenital health with adverse effects cumulative over time and not dependent on the age at menopause. A unique concern to the younger breast cancer patient who experiences menopause in her 20s, 30s, or early 40s is the loss of childbearing potential, a problem not as prevalent in women undergoing natural menopause who have usually completed their families. In select cases, counseling regarding the preservation of frozen embryos should be discussed before chemotherapy and the onset of menopause.

The use of estrogen replacement in breast cancer patients, especially during the first 5 years after diagnosis, is controversial; many physicians and their patients are reluctant to use this therapy although more practitioners are supporting estrogen use in select breast cancer patients after the consideration of informed consent, patient desires, and risk/benefit (1,2). The benefits of estrogen in women without breast cancer have been

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studied and are clear; however, the benefits versus risks are not as well-defined in breast cancer patients.

Alternatives to estrogen have not been researched as thoroughly because the advent of safe and effective hormone-replacement therapy regimens limited the need for nonestrogen management. The evaluation of alternatives to estrogen therapy has recently received expanded interest because there are subgroups of women in whom estrogen-replacement therapy is medically contraindicated, is not desired, is responded to inadequately, or is discontinued because of side effects: not all menopausal symptoms are related strictly to estrogen changes (3). Menopausal problems are not only caused by ovarian estrogen fluctuation and eventual decline but also by changes in other ovarian hormones and sociocultural beliefs and psychologic factors (4-6). In 1951, Donovan (7) was one of the first physicians who reported that some menopausal symptoms could be related to the psychologic health of the female. Data generated by social and behavioral scientists continue to underscore the marked input societal structure and the psychologic makeup the woman have on menopausal complaints (8-12). Therefore, menopausal symptoms should be evaluated in the context of the woman's age at menopause, socioeconomic class, religious affiliation, geographic location, education, and previous psychiatric history as well as her ovarian hormone status (13,14). For younger breast cancer patients who are menopausal, concerns other than hormonal decline are of importance because other factors (e.g., medical/surgical interventions necessitated by the malignancy, issues of mortality, possible disfigurement, etc.) affect overall health.

Menopausal problems directly related to ovarian function change can be classified into immediate (menstrual disturbances), short-term (vasomotor instability), long-term (osteoporosis and cardiovascular disease), and those possibly related to function (psychological, sexual, ovarian and other medical problems). Although estrogen-replacement therapy is potentially effective in treating all symptoms related to ovarian estrogen decline, each nonestrogen therapy is directed to the management of a specific complaint. However, some therapies may overlap and affect (either negatively or positively) other menopausal difficulties. After diagnoses of breast cancer, physicians should not dismiss nonestrogen treatments and should offer personalized counseling and therapies for management of climacteric sequelae to every patient.

Immediate Menopause Consequences: Menstrual Disturbance Treatment

One of the first symptoms women note before the occurrence of vasomotor symptoms is the interruption of menstrual cyclicity. During the early reproductive years, women typically menstruate every 25-35 days, experience uterine bleeding from 2 to 6 days, and lose less than 60 mL of blood. For 4 years or more before the actual cessation of menses, the length of a woman's menstrual cycle shortens by 2-3 days and bleeding is scantier, especially if no uterine pathology is present. With abnormalities of the uterus, such as adenomyosis or leiomyomas, bleeding may become heavier and prolonged. Because of ovarian follicular depletion, the number of anovulatory cycles

increases and cyclicity may be interrupted so that irregular bleeding patterns are common.

Nonestrogen methods utilized to regulate the cyclicity and/or amount of blood flow with menses include nonsteroidal, anti-inflammatory drugs, progestins, androgens, gonadotropin-releasing agonists, and endometrial ablation (15). Nonsteroidal anti-inflammatory drugs have been used to decrease the quantity of menstrual bleeding by up to 50% but have no impact on cyclicity (16,17). Progestins have been useful in the control of the menstrual cycle because failure to ovulate or inability to sustain adequate corpus luteum function or duration are often the etiology of the irregular menses. Progestins are powerful anti-estrogens that when used pharmacologically induce enzymes in endometrial cells that convert estradiol to estrone sulphate. Progestins diminish estrogen's effect on target cells by receptor-replenishment inhibition. Both of these factors account for the antimitotic, antigrowth impact of progestins on the endometrium. Medroxyprogesterone acetate and megestrol acetate, similar in structure to progesterone, are frequently used for the treatment of menstrual disturbances. Progestin therapy can either be prescribed monthly, cyclic, or used as needed by the patient with a typical dosage of 5-30 mg per day of medroxyprogesterone acetate for 10-14 consecutive days. Natural progesterone can be used intramuscularly (100 mg monthly) or intravaginally (25 mg 3 times daily for 10 days each month) (18,19). Progesterone vaginal suppositories are rarely used because of the frequency of dosing required and the cost. Norethindrone, norethindrone acetate, and norgestrel are three synthetic progestins that are structurally similar to androgens, but their adverse effects on lipids, particularly the decrease in high-density lipoprotein levels often reported at therapeutic doses, limit usefulness (19). Androgenic compounds, such as danazol, have antiestrogen effects and are used, but approximately 20% of women experience irregular uterine bleeding with therapy because of the atrophic endometrium induced (19). Endometrial ablation (Neodymium: Yttrium-Aluminum-Garnet laser and electrocoagulation) is a relatively new procedure and data are accumulating on the use of this technique as an aid in the treatment of menorrhagia (20).

Short-term Menopause Consequences: Vasomotor Instability Treatment

Hot flushes, night sweats, and insomnia are the most visible and, at times, the most disabling of the early problems facing the menopausal female. Up to 75% of menopausal women experience vasomotor symptoms and 15%-20% of affected women seek medical attention for therapy (21-23). Hot flushes are the consequence of the effects of sex hormone changes due to ovarian failure on hypothalamic neurotransmitter concentrations (24). Hot flushes have a direct impact on sleep pattern in that hot flushes are associated with waking episodes and estrogen-replacement therapy decreases sleep latency and increases rapid eye movement sleep. Because the vasomotor instability is related to estrogen, replacement of this hormone is an effective treatment and the standard against which other therapies are compared (25,26).

Although there is a placebo effect, objective recording of finger temperature and skin resistance has provided a quantifiable means of comparing the effects of various modes of therapy. Numerous methods had been tried or are currently in use to reduce the frequency of hot flushes; other drugs are in the research phases of evaluation (25). Sedatives such as phenobarbital and tranquilizers are often prescribed either alone or in combination with other drugs by healthcare providers for the treatment of hot flushes and other vasomotor symptoms. A commonly used preparation is a combination of 40 mg phenobarbital combined with ergotamine tartrate, a sympathetic inhibitor, and levorotatory alkaloids of belladonna, a parasympathetic inhibitor (27). This drug is effective for hot flushes with significant reduction of nervousness, palpitations, nausea, insomnia, dizziness, and irritability reported. Tranquilizers, which comprise a large group of drugs, are often used in the menopausal patient in the absence of a well-defined indication. In appropriate patients, tranquilizers are of value, especially in women who are excessively anxious, irritable, or have insomnia. Progestins, such as medroxyprogesterone acetate and megestrol acetate, have been successfully used in the treatment of hot flushes because of their ability to suppress the secretion of gonadotropins without altering the response of the pituitary to gonadotropin-releasing hormones (28). In addition, progestins alter the thermoregulatory set point, so that in addition to a hypothalamic site of action, they may act, in part, directly on the thermoregulatory center. The hot flush represents a sudden downward resetting of the set point and progestins, by raising the set point, make the thermoregulatory center more refractory to such stimuli (24,25,28). The benefit of progestins on hot flushes was first observed by Bullock et al. (29) who noted that hot flushes ameliorated in women with endometrial cancer who were treated with depo-medroxyprogesterone acetate. One hundred to 150 mg of depo-medroxyprogesterone administered monthly intramuscularly, or 10 mg daily medroxyprogesterone acetate or 40 mg of megestrol acetate administered orally are effective in suppressing hot flushes (30-33). Androgens have been tested with data derived from male subjects that support androgens, per se, independent of conversion to estrogen in the brain or other tissue, suppress flushes (32). It appears that androgens have a direct effect on the hypothalamus, but their efficacy on the control of hot flushes is not clearly defined (32,33).

Clonidine, an imidazoline derivative, has received attention as an alternative to estrogen for the treatment of hot flushes (34,35). Introduced in a low-dose form as an antimigraine drug and in a higher-dose form as an antihypertensive, clonidine was reported to reduce flushing in menopausal women, probably by inhibiting sympathetic nervous system function (36-39). This treatment, commonly given in the form of transdermal patches and best tolerated by hypertensive patients, can reduce hot flushes by 40% (34,35,40). Side effects include dizziness, dry mouth, fatigue, irritability, and nausea. Antidopaminergic drugs such as veralipride (100 mg daily) have also been reported as effective in the treatment of hot flushes (41). An adverse effect of the antidopaminergics has been the occurrence of galactorrhea and breast tenderness. Limited data on other nonestrogen drug treatments are conflicting in their superiority over placebo in the treatment of hot flushes. For instance, prostaglandin in-

hibitors such as naproxen, tricyclic antidepressants, and oxazepam have been tested for the relief of hot flushes, but the response does not seem to differ from placebo (42). Satisfactory success in controlling hot flushes has been noted with methyl-dopa, an aromatic amino acid decarboxylase inhibitor; this effect is probably mediated through the interference of catecholamine metabolic pathways (43). Reports of success with doses of 250-500 mg per day in normotensive women have been cited (43).

Another alternative to estrogen in the treatment of vasomotor symptoms may be the use of the synthetic steroid tibolone (Org OD 14), a compound with weak estrogenic, progestational, and androgenic activity (44). When given orally in doses of 2.5 mg per day, it is reported to have a beneficial effect on vasomotor symptoms such as hot flushes and excessive perspiration (44). Adverse effects from the drug have included weight gain and irregular vaginal bleeding.

Long-Term Menopause Consequences: Osteoporosis Treatment

Several nonestrogen treatments of osteoporosis are available and should be considered for high-risk younger women with breast cancer. Base-line screening to evaluate degree of risk by dual photon absorptiometry and then annual follow-up to assess effectiveness of therapy is advisable (45,46). The effects of weight-bearing exercise, walking, a lifestyle that minimizes trauma to the skeleton, and a low-protein diet with adequate calcium (1500 mg per day) and vitamin D (400-800 IU per day) have been found to be beneficial for the maintenance of skeletal health (47-51). A decrease in calcium absorption from the bowel occurs with normal aging and with the ingestion of oxalate-containing or high-protein foods (52,53). The increased acid formed from protein is buffered partially at the expense of bone minerals and diets that contain greater than 40 g per day of protein and may cause increased urinary excretion of calcium (52). Avoidance of excessive caffeine and alcohol, curtailment of tobacco use, as well as being slightly overweight, have been shown to have beneficial effects on bone (54-58). Some medications, particularly thyroid hormone, cholestyramine resin, tetracycline, bulk-forming therapeutic-fiber preparations, many furosemide diuretics, high doses of anticonvulsant drugs, and corticosteroids have a negative impact on bone (47,50,58,59).

Antiresorptive agents include estrogens, progestins, calcium, calcitonin, bisphosphonates, anabolic steroids, tibolone, calcitriol, tamoxifen, and thiazide diuretics. Stimulants of bone formation include sodium fluoride, parathyroid hormone, and growth factor. All drugs that increase bone formation are currently investigational.

Progestins that are effective in the relief of hot flushes can be used in osteoporosis prevention and treatment with or without estrogen. Several studies have demonstrated that the use of medroxyprogesterone acetate, megestrol acetate, and norethindrone reduce urinary calcium excretion and the urinary hydroxyproline-creatinine ratio and slow axial and appendicular bone loss (50-58,60-63). Medroxyprogesterone acetate at 5-20 mg daily, 19-norprogesterone at 500 mg daily, and depo-medroxyprogesterone acetate at 100-200 mg every 2-3 months have been

shown to be effective (60-63). The synthetic compound tibolone also appears to have a benefit of maintaining skeletal integrity (44). The anabolic steroids cause a decrease in bone mass in men when withdrawn, and data suggest that the administration of androgens may prevent bone loss in postmenopausal women (64,65).

Adequate dietary calcium or supplements, optimally taken with meals in divided doses of 1500 mg or higher, are beneficial as adjunctive measures when used with estrogen in maintaining postmenopausal skeletal health, but are not considered effective against menopausal-related bone loss if used alone. Accumulating data show that dietary calcium supplement, especially when combined with weight-bearing exercise in postmenopausal women, can slow bone loss at appendicular and axial skeletal sites (66-68). Calcium carbonate is frequently prescribed by health care providers because one tablet delivers 250 mg of elemental calcium. Although the addition of vitamin D increases the calcium balance by increasing calcium absorption, if used in doses of 1000 IU per day or higher, vitamin D or its metabolite increases urinary calcium excretion (69). The combination of calcium and vitamin D3 (cholecalciferol) was found to reduce the risk of hip fracture and other nonvertebral factors among elderly women (70). Fluorides, which are essential to the diet and believed to be necessary for normal skeletal growth, may be useful in preventing or treating osteoporosis. Although earlier reports on fluoride supplements noted an increased hip fracture rate, recent data suggest they may be beneficial to patients with osteoporosis (71-74). An intermittent treatment regimen to prevent refractoriness and adverse effects of 50-60 mg (enteric-coated capsules) per day is reported as a potent inhibitor of resorption; this therapy is optimal when used with calcium citrate, bisphosphonates, or calcitonin (75). Slow-release forms of sodium fluoride used with calcium citrate have also shown promise (76). Injectable synthetic salmon calcitonin is an inhibitor of osteoblast activity and has been shown to be potentially useful for the prevention of osteoporosis as well. Calcitonin is approved by the Food and Drug Administration for the treatment of established osteoporosis, showing short-term maximum efficacy (26 weeks) in slowing bone loss; over time an apparent resistance to drug action occurs. Synthetic salmon calcitonin at 50 IU subcutaneously every other day may be more efficacious than 100 IU subcutaneously daily (77). Research on the intranasal form of calcitonin shows the same increase in bone mineral content of the lumbar vertebrae after 6 months of use as with the injectable form (78,79).

Tamoxifen, effective in controlling disease in women with estrogen-receptor positive breast cancer metastases, may increase bone density (1,80). The bisphosphonates, such as etidronate disodium and Clodronate, are reported to be effective in maintaining skeletal integrity when used in an intermittent cyclical regimen (81-88). Research using growth hormone, which stimulates osteoblastic proliferation and differentiation in vitro, a therapy that may be available for future use (89,90). Promethazine hydrochloride, the seasonal use of thiazides, and ipriflavone are also being investigated for this purpose (91-93).

Long-Term Menopause Consequences: Cardiovascular Treatment

For women at high risk for cardiovascular disease in whom estrogen therapy is contraindicated, the emphasis on lifestyle change (e.g., exercise, low-fat diet, smoking avoidance, alcohol temperance, and weight control) has been encouraged. Women with hypertension or dyslipidemia should be encouraged to pursue treatment. The role of low-dose aspirin and tamoxifen in women appears promising. Data are available that report tamoxifen reduces total blood cholesterol by approximately 12% and low-density lipoprotein cholesterol by approximately 20% (94-96).

Long-Term Menopause Consequences: Atrophic Conditions Treatment

Urogenital atrophy has an impact on the medical and sexual well-being of the female. As vaginal atrophy progresses to atrophic vaginitis, complaints of pressure, irritation, pain, burning, dyspareunia, and a chronic malodorous discharge often occur. Estrogen loss to the bladder and uterus promotes relaxation of the supporting structures, therefore cystocele and uterine prolapse are more prevalent after menopause. With loss of estrogen to the urethral support, the incidence of urinary incontinence increases. The impact of these changes on younger women with breast cancer are more detrimental than for older menopausal women, since sexual activity and partner expectations are usually greater in younger women.

Systemic estrogen-replacement therapy has an impact on all estrogen-receptor positive tissue, not solely urogenital; the use of low-dose locally applied estrogen with minimal systemic absorption to reverse atrophy in the urogenital area is being researched. Nonestrogen-containing lubricants and moisturizers such as those with a polycarbophil base, assist in sexual comfort and eliminate or ameliorate annoying vaginal symptoms (97). Nonhormonal vaginal preparations are most effective when used in conjunction with continued sexual activity. Women who remain sexually active usually have less vaginal atrophy than those who are abstinent. Androgens have been shown to improve sexual desire and should be considered for breast cancer patients who complain of loss of libido (98). Kegel exercises, especially when uterine and bladder support are poor, and vaginal dilators, when urogenital atrophy is marked, may be beneficial and may be recommended. Self-stimulation can also be suggested to women, especially during coitally inactive periods, as a way of maintaining vaginal function (99).

Possibly Related Menopause Consequences: Psychologic, Sexual, Other Treatment

Whether ovarian changes have a direct effect on other symptoms associated with menopause, such as depression, listlessness, irritability, lack of self confidence, fatigue, feeling tense, forgetfulness, insomnia, restless legs, painful muscles/joints, shortness of breath, dizziness and palpitations, headache, etc., remains to be elucidated. Although it appears that women with hot flashes and sleep disturbance have more of these complaints, the impact of sociocultural and psychologic factors may

be substantial. Education and counseling regarding expected menopausal changes to remove fear, doubt, and negative attitudes are important. Encouraging healthy lifestyles will also favorably affect these symptoms. The etiology of specific complaints should be sought in women so that therapy can be individualized.

Alternatives

Before the availability of estrogen formulations, alternatives were the only treatments available for the management of menopausal consequences (100). Remedies that consisted of herbs, garlic, and onions, as well as stress management, biofeedback, acupuncture, and visualizations are listed as treatments of menopausal difficulties. There is a paucity of controlled studies regarding these methods of therapy and, in many instances, the medicinal use of herbs and other natural remedies has resulted in toxic side effects (101-103). Studies have shown that the use of dolomite as a "natural" calcium supplement may be harmful, since other elements (e.g., uranium, lead, arsenic, and cadmium) can be precipitated along with the desired elements at the time of formation. Bone meal preparations, if derived from the skeletons of old animals, may contain heavy metal pollutants.

Of all the commonly used home remedies, the use of vitamin supplements and garlic appears to have the most scientific support. Studies have shown that garlic and vitamin E may be useful in the prevention of cardiovascular diseases. Garlic decreases fibrinogen and fibrinopeptide levels, increases fibrinolytic activity, decreases serum cholesterol levels, and decreases the alimentary absorption of cholesterol and triglyceride (104). Prospective research suggests that vitamin E supplements are associated with a reduced risk of coronary heart disease in middle-aged woman (105). Vitamin B-6 (pyridoxine) at doses of 250 mg per day may alleviate menopausal symptoms such as depression, emotional instability, diminished sexual desire, and difficulty in concentrating (106). The use of herbs, especially in the treatment of hot flushes, insomnia, restlessness, and vaginal atrophy has been attempted. Herbs used in this regard include hawthorne, witch hazel, balm, and melilot (107).

Summary

Although estrogen-replacement therapy is the cornerstone of menopause management for symptomatic women and those at high risk for osteoporosis, cardiovascular disease, and urogenital atrophy, estrogen use in women with breast cancer regardless of age is controversial. There are a number of nonestrogen treatments prescribed for the management of menopausal symptoms, and they should be offered to breast cancer patients. The interaction of ovarian function, sociocultural environment, and psychological factors on menopausal symptoms should be discussed with each patient. As more data become available, defined protocols using nonestrogen treatment can be offered for specific menopausal complaints or problems.

There are several nonestrogen therapies that can be prescribed to younger breast cancer patients. For vasomotor symptoms, the combination preparation of phenobarbital at 40 mg, ergotamine tartrate at 0.6 mg, and levorotatory alkaloids of belladonna at 0.2

mg is effective. For osteoporosis, calcitonin is an approved alternative to estrogen and counseling and education should be reviewed on adverse personal habits and calcium and vitamin D requirements. The most promising new treatments that are now being investigated are the bisphosphonates, tamoxifen, and sodium fluoride. Counseling breast cancer patients on the role of tamoxifen should include the possibly beneficial bone effects of this drug as well as the potential lipid-lowering effects. Other preventive measures for cardiovascular disease should be discussed with women, and material on specific exercise programs and diets should be available for the patient to take home. Physician reference to vaginal lubricants and moisturizers and encouragement to remain sexually active for retardation of urogenital atrophy is important. In select cases, androgens may be considered, especially when loss of sexual desire occurs.

In summary, both the health care provider and the general public should be aware of the many nonestrogen alternatives for the treatment of menopausal symptoms, and dissemination of this information should be encouraged. Because of the importance menopause has in all women, especially younger women with breast cancer who become abruptly menopausal at a time when estrogen levels are in the reproductive range and in whom estrogen use is controversial, longitudinal prospective studies, such as the Women's Health Initiative sponsored by the National Institutes of Health, should be funded by the public and private sector. The role of ovarian failure and the impact of sociocultural and psychologic factors on specific menopausal symptomatology should also be scientifically assessed.

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Section VI: Psychosocial and Survival Issues

*Vincent Mor**

At this juncture, we are switching gears from the biological consideration of age to the social and psychological meaning of age.

Until now, speakers have repeatedly tried to define age in a manner that is consistent with the phenomenon they were studying. Thus, when the outcome of interest is survival, recurrence, or tumor response, age must be considered in a biologically relevant manner. We have seen that not only does the menopause represent a convenient way to cut the age distribution, but that very young women diagnosed with breast cancer appear to have higher mortality risk than even their middle-aged counterparts.

Indeed, the model presented earlier this morning suggests that the logarithmic rate of increase in breast cancer incidence before menopause and the linear rate of increase thereafter suggests both genetic and hormonal and aging influences on breast cancer incidence.

In contrast, if the outcomes of interest have social or psychological features, age must be considered in terms of its social meaning. Thus, studies of patterns of cancer treatment styles must consider the social influence of age, both on the woman's choices, as well as on the subtle influence that physicians and family members have on kinds of treatments ultimately delivered.

Those choices are influenced by the social and psychological view of age. Similarly, the social and psychological morbidities that are associated with breast cancer, which we will be hearing about this afternoon, must be viewed from a developmental and social role perspective.

Indeed, since socially accepted definitions of age appear to vary substantially from decade to decade, and between social and ethnic groups, cohort differences and ethnic differences must also be considered as we think about how to define age in a socially meaningful way.

The extent to which women experience significant social and psychological disruptions associated with breast cancer (e.g., reactions to false-positive mammograms, or electing hospice care in the terminal stage of the disease) may be greatly influenced by the various social roles they occupy.

For example, the child-rearing role of women in the United States now spans the late teens to early fifties. Thus, this social role has a very broad range with respect to age. This must be considered in understanding the effects of cancer on older and younger women. The competing demands of child rearing for many 50 year olds is irrelevant, but for some, older mothers will be catastrophic.

Similarly, employment-related income is crucial for many women well into middle age, particularly for single mothers. Any disruption of employment-related income is going to have a substantial influence at various points in the age cycle, but less so after retirement, which itself begins over a fairly broad time frame.

This afternoon, we will be hearing about the psychological, the social, the employment, and the economic disruptions that are associated with breast cancer and how each is influenced by the woman's age.

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Younger Women at Increased Risk for Breast Cancer: Perceived Risk, Psychological Well-being, and Surveillance Behavior

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The problem of breast cancer in younger women has received increased attention in recent years. As yet, however, little is known about the surveillance patterns and psychological characteristics of younger women who are at increased risk for this disease. This report presents a summary of preliminary data on risk perceptions, surveillance behaviors, and psychological well-being among women with a family history of breast cancer, with particular attention to younger women (under age 50). These data show that over three fourths of women aged 29 and younger hold the belief that they are likely to develop breast cancer; this finding was not significantly different in other age groups. Surprisingly, over one third of women aged 29 and younger had received mammograms; over one half of women aged 30-34 had mammograms; and over three fourths of women aged 35 and older had mammograms. As many as one half of women aged 35-39 had mammograms within the past year. Serious psychological morbidity was not noted in the samples; however, one third of women of all ages reported breast cancer worries that impair their daily functioning. Psychological distress was associated with nonadherence to mammography and with both infrequent and excessive breast self-examination practice. These data provide the basis for recommendations for research on breast cancer risk counselling for younger women. [Monogr Natl Cancer Inst 16:171-176, 1994]

A positive family history of breast cancer is the most important determinant of a woman's risk of developing this disease. Having one first-degree relative (FDR) with breast cancer imparts about a twofold to threefold increased risk, which increases to fivefold if the breast cancer in the FDR is bilateral (1). Risk also increases as the age of onset of breast cancer in the FDR decreases (2).

Recent studies highlighting the problem of early-onset breast cancer (3,4) have underscored the importance of counselling younger women at increased risk for this disease (5). As yet, however, little attention has been devoted to studying the psychological characteristics and surveillance behaviors of this subgroup of women. To address this gap in the literature, we conducted exploratory analyses of data in three convenience samples of women with family history of breast cancer. The ob-

jective was to compare risk perceptions, psychological symptoms, breast cancer worries, and breast cancer surveillance patterns of women in different age groups. Also, we evaluated the associations between psychological variables and breast cancer surveillance patterns among women under age 50. These data provide the basis for recommendations for behavioral research to promote adherence and psychological well-being among younger women at an increased risk for breast cancer.

Description of Study Samples and Ascertainment Procedures

Fox Chase Cancer Center (FCCC)

This sample included 179 females, 30-75 years of age, who had a family history of breast cancer in at least one FDR. Women who had had a prior diagnosis of cancer (except basal cell or squamous cell skin cancers) were excluded. Potential subjects were identified initially by their relatives who were being followed for breast cancer at FCCC. Program staff approached the index breast cancer patients during a routine clinic visit or by telephone shortly after their appointments. Patients were asked for permission to contact their sisters, daughters, and/or mothers regarding participation in a 15-minute telephone interview (response rate, 98%).

The respondents in the FCCC sample were predominantly white (92%), and 37% had education beyond high school. Twenty-three percent were aged 30-34, 26% were aged 35-39, 25% were aged 40-49, and 26% were aged 50 or older. In terms of major breast cancer risk factors, 91% had one FDR affected with breast cancer (the rest had two or more), and the mean age at diagnosis of the index patient was 51 (SD = 13.0). Fourteen percent of subjects reported a previous breast biopsy; this was more likely among women aged 50 and older (Fisher exact test = 12.2; $P = .04$). The distribution of other risk factors did not differ significantly across age groups.

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See "Notes" section following "References."

Johns Hopkins Oncology Center (JHOC)

This sample included 238 females, aged 20-75, with a family history of breast cancer, who were identified primarily through index breast cancer patients or through physician referral. Self-report questionnaires were completed by subjects before an initial visit at the JHOC Breast Surveillance Service (response rate, 70%). The JHOC respondents were predominantly white (96%), and 61% had education beyond high school. Eighteen percent were aged 20-29, 18% were aged 30-34, 17% were aged 35-39, 32% were aged 40-49, and 16% were aged 50 or older. In terms of major risk factors, 79% had one FDR affected with breast cancer (the rest had two or more), and the mean age at diagnosis of the index patient was 49 years ($SD = 14$). Subjects aged 50 or older reported later onset of breast cancer in their FDRs compared with subjects 34 years of age or younger (mean age at diagnosis of the index patient, 52 versus 46, respectively; $P = .05$). Thirty-two percent of subjects reported a previous breast biopsy. Subjects aged 50 or older more frequently reported a previous biopsy than those 39 or younger (chi-square test = 4.82; $P = .05$).

Strang Cancer Prevention Center (SCPC)

The SCPC sample included 363 subjects, aged 20 and older, who were self-referred to the SCPC and completed self-report questionnaires before their initial visit (response rate, 73%). The SCPC respondents were predominantly white (90%), and 83% had education beyond high school. Seven percent were aged 20-30, 15% were aged 30-34, 19% were aged 35-39, 33% were aged 40-49, and 26% were aged 50 and older. In terms of major risk factors, 34% of SCPC subjects had one FDR with bilateral premenopausal breast cancer, 45% had one affected FDR plus one affected second-degree relative, and 21% had two or more affected FDRs. The mean age at diagnosis of the affective FDRs was 47 years ($SD = 11$). Subjects, aged 50 or older, reported later age of onset in their FDRs compared with subjects aged 39 and younger (mean age, 56 versus 45 years, respectively; $P < .001$). Thirty-six percent of subjects had a previous breast biopsy. Women aged 50 or older were significantly less likely to report a previous breast biopsy than women aged 39 and younger (24% versus 50%, respectively; chi-square test = 13; $P = .01$).

Measures

Risk Perceptions

Likert-style items were used to measure perceived relative risk (rated as 1 = "much lower than average" to 5 = "much higher than average") (FCCC) and perceived likelihood of developing breast cancer (rated as 1 = "not at all likely" to 5 = "extremely likely") (JHOC/SCPC). Chi-square tests of association were conducted to identify age-related differences in perceptions of breast cancer risk.

Breast Cancer Surveillance

In all three samples, categorical response items were used to measure the time since the last mammogram and the frequency of breast self-examination (BSE). Descriptive statistics were

generated to characterize the breast cancer surveillance practices of women in the different age groups.

Psychological Well-being

Two types of psychological measures were employed: generalized psychological symptoms and breast cancer-specific psychological symptoms. Measures of generalized psychological symptoms used in the different samples included the following: (a) Brief Profile of Mood States (POMS) (6), an adjective checklist which measures level of mood disturbance (JHOC); (b) Mental Health Inventory (MHI) Depression Scale (7), a four-item Likert-style measure which assesses generalized depression (FCCC); and (c) Brief Symptom Index (BSI), a Likert-style instrument which measures global psychological distress (8) (SCPC). Analysis of variance (ANOVA) methods were used to identify age-related differences in generalized psychological symptoms and to explore associations between psychological factors and surveillance practices.

Psychological symptoms related specifically to breast cancer risk also were examined in the different samples using the following: (a) The Revised Impact of Events Scale-Intrusion Subscale (RIES) (9), an 11-item Likert-style measure that assesses the frequency and severity of intrusive thoughts and feelings related to a specific event (i.e., having a family history of breast cancer) (FCCC), and (b) Breast Cancer Worry, two individual Likert-style items used in previous research (10,11), were employed to measure the severity of breast cancer worries (rated as 1 = "no problem" to 7 = "severe problem") (JHOC) and the impact of breast cancer worries on daily functioning (rated as 1 = "not at all" to 4 = "very much") (FCCC). ANOVA methods were used for continuous measures of breast cancer-specific distress (i.e., RIES), and chi-square tests were used for categorical measures (i.e., breast cancer worries).

Results

Risk Perceptions

The frequencies and proportions of women who perceived themselves as having a higher risk and those who believed themselves to be likely to develop breast cancer are shown in Table 1. In the FCCC sample, over two thirds of women under age 50 perceived themselves to be at high risk for developing breast cancer. These rates are comparable to those in women in the JHOC and SCPC samples. In the FCCC sample, women aged 30-34 and those aged 50 and older were less likely to perceive themselves as having an elevated risk than were women in other age groups (chi-square test = 18.9; $P = .01$). In the JHOC and SCPC samples, there were no significant age-related differences in risk perceptions. However, it is notable that about three fourths of women aged 29 and younger believed that they are likely to develop breast cancer someday.

Breast Cancer Surveillance

Comparisons for rates of "ever having a mammogram" for women in the different age groups also are shown in Table 1. Surprisingly, about one third of women aged 29 and younger in the JHOC and SCPC samples had obtained mammograms.

Table 1. Perceived risk and breast screening variables by age group

Variable	Age group, No. (%)				
	<30 y	30-34 y	35-39 y	40-49 y	≥50 y
Perceived risk					
Believe risk higher than average*	—	27 (64)	38 (83)	36 (80)	25 (54)
Believe likely to develop breast cancer†	30 (71)	34 (81)	31 (74)	59 (79)	26 (69)
Believe likely to develop breast cancer‡	20 (77)	45 (79)	51 (75)	92 (77)	62 (65)
Mammography					
Ever had*	—	24 (57)	35 (76)	40 (89)	40 (87)
Ever had†	13 (31)	36 (86)	41 (98)	73 (97)	38 (100)
Ever had‡	9 (35)	39 (68)	58 (89)	101 (100)	91 (100)
Breast self-examination					
Less than once/mo*	—	14 (33)	5 (11)	17 (38)	11 (24)
Once/mo	—	12 (29)	26 (56)	14 (31)	15 (32)
Greater than once/mo	—	16 (38)	15 (33)	14 (31)	20 (44)
Less than once/mo†	22 (52)	18 (43)	17 (41)	28 (37)	16 (43)
Once/mo	17 (40)	19 (45)	14 (33)	35 (47)	17 (46)
Greater than once/mo	3 (8)	5 (12)	11 (26)	12 (16)	4 (11)
Less than once/mo‡	19 (74)	40 (71)	50 (74)	76 (63)	47 (49)
Once/mo	3 (13)	14 (25)	15 (23)	37 (31)	40 (42)
Greater than once/mo	3 (13)	2 (4)	1 (3)	7 (6)	9 (9)

*FCCC, sample of FDRs of breast cancer patients (n = 179).

†JHOC, sample of FDRs of breast cancer patients (n = 238).

‡SCPC, sample of self-referred women (n = 363).

Among women aged 30-34, rates of ever having mammograms ranged from 57% to 86%. In all three samples, over three fourths of women aged 35 and older had ever had mammograms.

Fig. 1 shows the proportions of women who reported having mammograms in the past year. For example, among women aged 29 and younger in the JHOC and SCPC samples, 14% and 31%, respectively, had mammograms in the past year. The proportions of women having mammograms in the past year ranged from 24% to 35% for women aged 30-34 and from 40% to 50% for women aged 35-39.

Self-reported BSE frequency is shown in Table 1. Among women aged 29 and younger, about one half to three fourths of

women reported practicing BSE less often than once per month. In the 30 to 34 year age group, these figures ranged from 33% to 71%. Interestingly, the highest rates of nonadherence to monthly BSE were found among the self-referred women in the SCPC sample. Overall, 72% of women aged 39 and younger in this sample practiced BSE less than once per month. Also notable in the FCCC sample is the finding that over one third of women in all age groups reported practicing BSE more frequently than once per month.

Psychological Well-being

As shown in Table 2, measures of mood disturbance (POMS) and depression (MHI) failed to reveal significant age-related differences in psychological distress among women in the JHOC and FCCC samples. Moreover, the levels of depression and mood disturbance observed in these samples are comparable to those in the general population (7,12). The measure of global psychological distress (BSI) was administered to women in the SCPC sample. As reported previously (13), the levels of distress observed in this sample, as a whole, were significantly elevated relative to the general population. Analyses by age group show that the highest levels of global psychological distress were among women aged 29 and younger ($P = .002$).

Breast cancer-specific psychological symptoms also are shown in Table 2. Levels of intrusive thoughts were found to be significantly higher among women aged 50 and older than among women in the younger age groups ($P = .05$). However, as reported previously (14), women in all age groups reported levels of intrusive thoughts that were comparable to those observed in populations exposed to a traumatic stressor (9). With regard to breast cancer worries, the severity of worries among women in the JHOC sample did not vary by age group. However, age-related effects were observed in the FCCC sample for

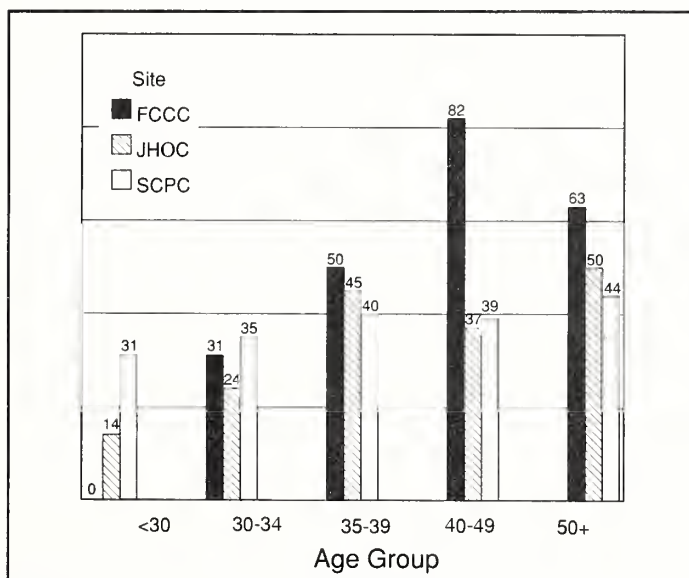


Fig. 1. Proportion of women reporting mammograms in the past 12 months by age.

Table 2. Psychologic variables by age group

Variable	Age group, mean (SD)					P
	<30 y	30-34 y	35-39 y	40-49 y	≥50 y	
Generalized symptom						
Depression (MHI)* (range, 5-20)	—	10.6 (3.6)	10.3 (3.6)	10.3 (4.0)	11.7 (4.1)	ns§
Mood disturbance (POMS)† (range, 0-44)	9.7 (7.0)	13.1 (8.9)	10.4 (10.0)	8.9 (4.5)	10.0 (6.7)	ns§
Global symptom index (BSI)‡ (range, 0-3.7)	0.91 (0.58)	0.63 (0.44)	0.49 (0.42)	0.64 (0.66)	0.44 (0.53)	.002
Breast cancer-related symptoms						
Intrusive thoughts (RIES)* (range, 0-35)	—	12.1 (10.1)	12.2 (10.4)	13.2 (11.3)	18.5 (11.8)	.03
Worries as a problem† (range, 1-7)	2.79 (1.52)	3.09 (1.61)	3.40 (1.97)	3.11 (1.57)	3.04 (1.62)	ns§
Worries affecting daily functioning‡ (range, 1-4)	—	1.68 (0.93)	1.36 (0.71)	1.27 (0.73)	1.84 (1.0)	.003

*FCCC, sample of FDRs of breast cancer patients (n = 179).

†JHOC, sample of FDRs of breast cancer patients (n = 238).

‡SCPC, sample of self-referred women (n = 363).

§ns = not significant.

the impact of worries on daily functioning ($P = .003$). The highest levels of worry-related impairment were observed among women aged 30-34 and those aged 50 and older—42% of women aged 30-34 and 49% of women aged 50 and older reported breast cancer worries that had at least “a little” effect on their daily functioning, compared with 20% of women aged 35-49.

Psychological Responses and Surveillance Practices

The final set of analyses used ANOVA methods to explore the relationships of the psychological variables to adherence to mammography and BSE among women aged 49 and younger. To examine mammography practices, a binary “adherence to mammography” variable was created using age-specific mammography guidelines that were in practice at the time of the surveys. That is, women aged 35-39 were considered “adherers” if they had at least one mammogram (i.e., a “baseline”), and those aged 40-49 were “adherers” if they had a mammogram within the past 1-2 years. Because of the absence of guidelines for women aged 34 and younger, these subjects were excluded from this set of analyses. All subjects aged 49 and younger were included in the analyses of BSE adherence. The mean scores for statistically significant comparisons are presented below (see Table 2 for ranges of scores for psychological measures).

The associations between psychological distress and breast cancer screening practices varied by measure (i.e., psychological instrument) and study population. In the FCCC sample, intrusive thoughts showed an inverse association with mammography adherence; that is, women who had not had a mammogram according to age-specific guidelines had higher levels of intrusive thoughts than women who had adhered (mean RIES scores = 16.7 versus 11.8; $P = .05$). By contrast, in the JHOC sample, women who had not had a mammogram in the past year had lower levels of breast cancer worries compared with those who had received one (mean worry scores = 2.99 versus 3.61; $P = .001$). None of the generalized distress measures (i.e., MHI, POMS, and BSI) were found to relate to mammography adherence.

Two psychological variables were found to be associated with BSE frequency. As reported previously in the SCPC sample

(13), levels of generalized psychological distress were highest among women who never practiced BSE or practiced less than once per month, compared with women who practiced once per month or more (mean BSI scores = 0.86, 0.64, and 0.51, respectively; $P = .04$). By contrast, in the FCCC sample, levels of intrusive breast cancer thoughts were highest among women who practiced excessively (i.e., more than once per month) than those who practiced once per month or less (average RIES scores = 16.6 versus 10.0; $P = .008$).

Discussion of Preliminary Data

Perceived Risk

In the three samples examined, a majority of younger women, including those aged 29 and younger, perceived their risk to be above average and believed that they were likely to develop breast cancer. This finding is consistent with a previous study that showed that women aged 35 and older with a family history of breast cancer perceive themselves as more vulnerable to breast cancer than women of comparable age without a family history (15).

While these women are able to identify themselves as being at “increased risk,” there is a concern that many are overestimating their actual risk of breast cancer. For example, both anecdotal and empirical data indicate that as many as one half of women with a family history of breast cancer overestimate their risks (16-18). In one study of FDRs of breast cancer patients, 80% estimated their lifetime breast cancer risk to be five in 10 or greater, despite the fact that the average estimated lifetime risk in the sample was 12% (18). In another study, only 11% of women with a family history of breast cancer were able to identify their lifetime risks accurately, and 47% overestimated their risks (17). These findings underscore the importance of educating younger women to promote accurate appraisals of personal breast cancer risks.

Surveillance Behaviors

In the samples examined, a majority of women aged 39 and younger had received mammograms, and many of them participated in screening on a regular basis. Recent mammograms

were reported by about one fifth of women aged 29 and younger, one third of women aged 30-34, and one half of women aged 35-39. Despite this, only a minority of women of all ages reported monthly BSE practice.

While normative data on the screening practices of younger women in the general population are not available, these results can be compared with those obtained in samples of women aged 35 and older. For example, among women aged 35-39 who participated in a screening program conducted in 1987, only 22% of those with a family history of breast cancer and 11% of those without a family history had ever had a mammogram (15). Among women 40-49, about 35% of those with or without a family history had previous mammograms. A review of recent studies indicates that fewer than one third of women in the general population obtain mammograms on a regular basis (19). The higher rates of mammography use in the present samples may be attributable, in part, to the fact that the vast majority of subjects had a higher socioeconomic status.

Nevertheless, the observed mammography patterns of younger women in these samples are somewhat surprising, given the absence of mammography guidelines for women in these age groups. Moreover, recent reports suggest that the benefits of regular mammography in younger women may not outweigh the possible risks (20). This is a particular concern, since it is likely that many of the women in the JHOC and FCCC samples did not carry a strong inherited risk of breast cancer—the vast majority had only one affected FDR and no previous breast biopsies. This is consistent with previous studies of women at increased risk of breast cancer, which suggests that perceptions of vulnerability may be a stronger determinant of mammography use than objective risk status (15,21,22).

Psychological Well-being

With regard to psychological well-being, the responses among younger women were found to be similar to those among older women. The single exception to this finding was in the sample of SCPC women, where significantly higher levels of distress were found among women aged 29 and younger. One interpretation of this finding is that, among younger women, only those with very high levels of risk and/or anxiety will be motivated to self-refer to a breast cancer screening program.

It is notable that high-risk women of all ages in the FCCC and JHOC samples reported breast cancer worries that were perceived as problematic. Thus, while serious psychological morbidity may not be prevalent in the general population of younger women at increased risk, many of these women may have breast cancer worries that have the potential to compromise their daily functioning.

Psychological Distress and Surveillance

The results of this analysis suggest that the associations between psychological distress and mammography use in younger women are fairly complex. Mammography adherence was reduced among women who scored higher on a clinical measure of intrusive thoughts [i.e., RIES (9)] but enhanced among those who scored higher on a single-item measure of breast cancer worries [i.e., developed by Stefanek and Wilcox (10)]. The motivating effect of breast cancer concerns (11) and the deter-

rent effect of more serious psychological distress (14) have been noted previously in studies of mammography practices of women at increased risk. To explain these findings, it has been suggested that intermediate anxiety levels may be optimal for activating surveillance behaviors in this population (23).

With regard to BSE, two potential problems were identified. First, a subset of younger women was practicing BSE excessively, and this was related to intrusive thoughts about developing breast cancer. Second, many younger women were practicing too infrequently. The highest rates of nonadherence to monthly BSE were found among the SCPC self-referred sample. As reported previously (13), adherence to BSE was significantly reduced among women who scored higher on a clinical measure of global psychological distress (8). Thus, the high levels of risk and anxiety and psychological distress which prompt these women to self-refer to a breast cancer screening program may also deter them from BSE practice.

Limitations of Results

The results presented here should be considered preliminary. Variation between samples in methods of recruiting high-risk subjects (i.e., self-referred versus population-based) as well as between and within sample variation in risk profiles makes it difficult to draw conclusions about the associations between psychological factors and surveillance behaviors. Also, there is a need to cross-validate the psychological instruments in different populations and to employ adequate control samples. Finally, since all samples were demographically homogeneous (i.e., white, educated), these results may not be generalizable to less educated or minority women at increased risk of breast cancer.

Recommendations for Future Research

The results presented here point to a need to develop approaches to counselling younger women at increased risk for breast cancer. The objectives of these programs would be to promote accurate appraisal of personal breast cancer risk, to encourage appropriate use of breast cancer screening modalities, and to reduce breast cancer worries that may compromise quality of life among younger women.

Randomized clinical trials will be essential to evaluate the impact of breast cancer risk counselling on younger women. Risk perceptions, psychological responses, and surveillance patterns should be evaluated at multiple timepoints. These include before risk counselling, immediately after counselling, at short-term follow-up (i.e., 1-3 months), and at long-term follow-up (i.e., 1-5 years) (24). Ideally, trials should evaluate the relative impact of programs that vary in terms of the mode of presentation of risk information, the structure of the interventions, and the timing of delivery. For example, risk information may be presented in a variety of ways. These include providing lifetime risk estimates for the development of breast cancer (25,26), providing relative risks for individual risk factors (27), or offering qualitative risk labels (e.g., moderate risk, high risk) (16). As yet, however, little is known about the impact of mode of risk presentation on comprehension and psychological and behavioral outcomes.

Variables that moderate the impact of breast cancer risk counselling in younger women also should be identified. In two recent studies of women at increased risk, the effects of psychological factors on participation in prevention and screening activities differed according to the educational level of individual women (14,28). This underscores the importance of including subjects of diverse socioeconomic backgrounds in studies of breast cancer risk counselling. In addition, individual differences in personality and coping styles may also influence psychological well-being and behavior among women at increased risk (29,30). The identification of psychologically vulnerable subgroups of younger women, based on their sociodemographic and psychosocial profiles, might be very useful in targeting breast cancer risk counselling interventions to women's individual needs.

The issues raised here are likely to become increasingly complex as genetic testing for breast cancer susceptibility is integrated into clinical practice (5,31). A majority of women who request genetic testing for breast cancer susceptibility are likely to be younger women with high levels of anxiety about their personal breast cancer risk (30). The rapid pace of research on the molecular biology of breast cancer makes this an optimal time to develop ethical and effective strategies for obtaining informed consent and for communicating genetic information about breast cancer to younger women.

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Notes

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Sexuality and Body Image in Younger Women With Breast Cancer

Leslie R. Schover*

Breast cancer has the potential to be most devastating to the sexual function and self-esteem of premenopausal women. Nevertheless, not one study has systematically compared the impact of breast cancer treatment on sexual issues across age groups. Research shows that younger women with breast cancer have more severe emotional distress than older cohorts. In a group of patients seeking sexual rehabilitation in a cancer center, younger couples were more distressed, but also had the best prognosis with treatment. In theory, loss of a breast or poor breast appearance would be more distressing to women whose youth gives them high expectations for physical beauty. Seeking new dating relationships after breast cancer treatment is a special stressor for single women. Potential infertility also may impact on a woman's self-concept as a sexual person. Systemic treatment disrupts sexual function by causing premature menopause, with estrogen loss leading to vaginal atrophy and androgen loss perhaps decreasing sexual desire and arousability. Research on mastectomy versus breast conservation across all ages of women has demonstrated that general psychological distress, marital satisfaction, and overall sexual frequency and function do not differ between the two treatment groups. Women with breast conservation do rate their body image more highly and are more comfortable with nudity and breast caressing. There is some evidence that breast conservation offers more psychological "protection" for younger women. Research on the impact of breast reconstruction is sparse, but reveals similar patterns. Future studies should use rigorous methodology and focus on the impact of premature menopause and the effectiveness of sexual rehabilitation for younger women. [Monogr Natl Cancer Inst 16:177-182, 1994]

A diagnosis of breast cancer at any age may trigger a woman's fears about losing her desirability or capacity for sexual pleasure. The younger the woman, however, the greater the potential impact of the cancer treatment on her reproductive life. Loss of a breast or scarring from surgery and radiotherapy may seem intolerable to a young woman who has not yet dealt with the impact of childbearing or aging on her body. Women who are unmarried fear that a potential mate will reject them, not only because of physical imperfection, but out of fear of a cancer recurrence. Those who have not finished childbearing have concern that a pregnancy could increase their risk of recurrence or that systemic treatment will render them permanently

infertile. Some women may be pregnant or have babies who are breastfeeding, so that the cancer interferes with their ability to nourish their child. Early in a pregnancy a woman may be faced with the anguish of deciding whether to have an abortion or to put her life at unknown risk by postponing cancer treatment. Reproductive losses can decrease a woman's interest in sex because lovemaking evokes a sense of grief instead of joy.

The young woman with breast cancer is also increasingly a candidate for systemic treatment. Premature ovarian failure after chemotherapy can contribute to dyspareunia and perhaps to loss of desire for sex. The sexual side effects of chemotherapy and hormonal treatment for breast cancer have largely been ignored until very recently.

Despite these commonsense observations, researchers have ignored age as a moderating variable in studying the impact of breast cancer and its treatment on women's sexuality. Some data suggest that younger women are generally more psychologically distressed than older women by a diagnosis of breast cancer (1-4). The age difference makes sense given the many tasks that a younger woman has to accomplish, despite the anxiety of having her life at risk and the discomfort of cancer treatment. Little specific information is available on age and sexuality. Within a small group of self-selected, middle-class mastectomy patients, Jamison et al. (5) found that younger women rated their surgery as a more negative influence on their sexual relationships. All of the women in their sample were over age 40. In a larger and more representative group of 274 women with breast cancer studied by Vinocur and colleagues (3), few women in any age category reported sexual problems. Within a group of 76 women with cancer at varying sites (most pelvic tumors) who sought sexual rehabilitation in a cancer center (6), younger patients were more psychologically distressed in general. Yet, the younger patients also had better outcomes when their sexual dysfunctions were treated.

In the absence of adequate data on age and sexuality in women with breast cancer, this paper reviews several relevant topics: the impact of breast conservation versus mastectomy on women's sexual lives, the effect of breast reconstruction in improving sexual satisfaction, sexual function after systemic therapy for breast cancer, the need for rigorous methodology in this research area, and issues of most importance for future research.

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Mastectomy Versus Breast Conservation and Sexuality

A number of studies have compared quality of life in women who had modified radical mastectomies or breast-conserving surgery (usually with radiotherapy) (1,7,8). Despite methodological flaws, including small sample sizes, often nonrandom assignment of women to treatment groups, idiosyncratic assessment instruments, nonstandard intervals of follow-up since surgery, lack of specification of menopausal status, and inattention to the impact of adjuvant systemic treatments, the conclusions across studies are remarkably similar. Psychological adjustment, whether measured in terms of major psychiatric disorders or general levels of emotional distress, does not differ between treatment groups (9-21). Marital satisfaction or divorce rates also are quite similar in breast conservation and mastectomy patients (4,9-11,13,14,19). There is little evidence that the experience of breast cancer disrupts stable marriage relationships. When patients are asked to rate current frequency of sexual activity or changes in sexual frequency from before to after cancer treatment, no group differences emerge (15,16,18,22). Rates of sexual dysfunction do not differ in most studies by extent of surgery, whether measured in terms of one question on "sexual problems" (12,14,18,20) or several items measuring lack of desire, poor arousability, orgasmic disorder, or dyspareunia (15,21,22). In general, only a minority of women experience a decreased frequency of sex or specific sexual dysfunctions.

Studies that show a benefit of breast conservation on sexuality are most typically those that use more subjective questions, i.e., a rating of sexual "enjoyment," (4,23) or of comfort with nudity or breast caressing in a sexual situation (16,20-22). Questions about body image also demonstrate that women with less extensive surgery feel more attractive and sexually desirable than those who have mastectomy without breast reconstruction (9,13,15,16,18,19,23). The advantage of breast conservation in promoting a positive "body image" is seen despite the lack of clear conceptualization of this variable, much less a well-designed, standardized inventory to measure it (24).

There is a surprising lack of attention to age as a moderator of women's reactions to the extent of breast surgery. The great majority of studies treat age only as a variable that should be matched in comparing groups of women undergoing mastectomy or breast-conservation surgery. Pozo and colleagues (4) noted that younger women were the most distressed patients in both the mastectomy and breast-conservation treatment groups. Another study noted that women who had had conservation surgery were less psychologically distressed at 18-month follow-up than those who had had mastectomy, but only within the group of women under age 40. Unfortunately, no assessment of sexual function or satisfaction was included in the protocol (17).

Age could influence the question of whether the opportunity to choose between mastectomy and breast conservation confers a benefit in terms of overall psychological adjustment or sexual satisfaction. Younger women have grown up in an era of health consumerism and may expect to play a more assertive role in their health care. They could also have more knowledge about breast cancer and its treatments than older women, given the increased media attention to this disease in recent years. Follow-

field et al. (25) assessed a group of 269 women with stage I or II breast cancer who either were advised by their surgeon to have a specific operation or were given a choice of surgery. All women who chose mastectomy over breast conservation were over age 50. Those women who had a choice were less depressed at 1-year follow-up. In general, however, women with mastectomy versus breast conservation did not differ at the final assessment point in their desire for sex, with about 30% of women reporting decreased desire since the diagnosis of breast cancer. Another recent comparison of women undergoing mastectomy with and without a choice of breast-conservation surgery also found no differences in sexual satisfaction at follow-up (4). An analysis of age effects in these samples would have been interesting.

Breast Reconstruction and Sexuality

Anecdotal reports suggest that younger women are more likely to choose breast reconstruction after mastectomy, but no systematic studies of age and breast reconstruction are available (26). In fact, data on sexual function and body image after breast reconstruction are not as extensive as one would expect (8). Research suggests, as with breast conservation, that body image is more positive after breast reconstruction compared with mastectomy alone (27-30). Women appreciate the ability to wear a wider range of clothing and feel greater comfort with appearing nude in front of their sexual partner. In one survey, women who had nipple reconstruction as part of the procedure were happier with erotic breast sensation and tissue softness than were women who only had breast mounds (31). Of course, there is no physiological basis for these perceptual differences between groups. Women who have immediate reconstruction are just as satisfied with their cosmetic results as women who experience the impact of the mastectomy, delaying reconstructive surgery (29,30).

The impact of breast reconstruction on sexual frequency or satisfaction is less clear. In one study, most women who had sexual problems were the younger ones who had delayed reconstruction (29). Their satisfaction with sex improved after reconstructive surgery. In another comparison, without reference to age, there was no difference in the frequency of sex between women who received immediate breast reconstruction as part of a randomized protocol and those on the waiting list to receive surgery after a year's delay (27). It would be helpful to know if women who have mastectomy with reconstruction are as satisfied, as a group, as women who have breast-conservation surgery. Only one comparison has been made, and the sample was quite small, but showed that the reconstruction group was less satisfied with their sex lives than the breast conservation group at 6-month follow-up (4). This difference disappeared by 1 year, however, which could reflect increased satisfaction as the reconstruction process was finished, and healing took place. Again, age effects are not systematically examined in these studies.

Systemic Therapy and Sexuality

The focus on breast mutilation and its psychosexual sequelae has obscured a crucial factor in women's sexual function after

treatment for breast cancer—the impact of systemic treatment (2,8,25,32). For women who are premenopausal, combination chemotherapy or hormonal manipulation may impair quality of life far more severely than the localized treatment for a breast tumor.

Combination Chemotherapy

Despite increasing use of combination chemotherapy as adjuvant treatment of premenopausal women with breast cancer, its morbidity in terms of infertility and sexual dysfunction is only known in general terms. Ovarian failure after chemotherapy is related to dose and type of drug, with alkylating agents having the most severe impact (33,34). Women who are over age 35 when treated are more likely to have permanent menopause than are younger women. Follow-up studies of women treated for Hodgkin's disease suggest that even those who recover menses may be at risk for premature menopause in the future (33). In addition to arresting follicular maturation, and in more severe cases, destroying ova and follicles, chemotherapy regimens disrupt hormone production by the ovaries. Circulating levels of estrogens are decreased, accompanied by elevated levels of follicle-stimulating hormone and luteinizing hormone (33). The clinical symptoms of premature menopause include the sudden onset of hot flashes, vaginal dryness, and atrophy, often with more severe discomfort than would be seen with natural menopause. Dyspareunia is very common in women with premature menopause. Over-the-counter lubricants such as Astroglide (BioFilm Inc., Vista, Calif.), Lubrin (Kenwood Laboratories, Fairfield, N.H.), or Replens (Columbia Laboratories, Inc., Miami, Fla.) compensate for lack of lubrication, but the thin and fragile vaginal mucosa may still be irritated by sexual intercourse. Given the role of long-term estrogen deficiency in the genesis of osteoporosis and cardiovascular disease (35,36), the American College of Obstetricians and Gynecologists recently suggested that replacement estrogens be considered for some breast cancer survivors (37). They advocated that gynecologists make individual decisions based on a woman's risk profile for cancer recurrence, eliciting her informed consent and the guidance of her oncologist.

Clinical experience suggests that chemotherapy contributes to sexual dysfunction in several other ways that have not been the subject of research. Postmenopausal vaginal atrophy is associated with recurrent urinary tract infections or vaginal monilial infections. Episodes of these painful conditions may be triggered by sexual intercourse. Drugs that cause stomatitis often cause periodic vaginal irritation during active treatment. Women report episodic severe dyspareunia and the presence of whitish plaques on the vulva. Women with genital herpes virus or the human papilloma virus can experience exacerbations when immunosuppressed by chemotherapy. Of course, the alopecia, weight gain, and pallor often associated with chemotherapy can temporarily make women feel very unattractive. Losing pubic hair is a temporary embarrassment that inhibits many women sexually.

One other hormonal change that may occur with chemotherapy is a decrease in circulating androgens (32). In women, as well as in men, androgens act in the brain to promote sexual desire (38,39). About 50% of circulating androgens are of

ovarian origin, while the rest are produced by the adrenal glands. After natural menopause, levels of adrenal androgens appear stable, while the ovarian androgens gradually decrease (32). Most women maintain normal levels of sexual desire after natural menopause (40), but after premature ovarian failure or ablation, the loss of androgen production may be severe enough to interfere with a woman's desire and arousability. Sherwin (39) demonstrated that after bilateral oophorectomy for benign disease, androgen supplementation is superior to estrogen alone in restoring sexual desire and elevating general mood, although it has little impact on orgasmic capacity. Sherwin believes that upward fluctuations in brain levels of androgens, rather than tonic androgen levels, may be responsible for maintaining sexual desire.

Kaplan (32) has applied this work to breast cancer patients treated with chemotherapy. In a small clinical case series, 10 of 23 such women who presented with complaints of low sexual desire had abnormally low levels of circulating testosterone after chemotherapy for breast cancer. Androgen supplementation has been helpful to a subgroup of the women. Kaplan suggests that postchemotherapy patients with complaints of sexual dysfunction have testing for total and free serum testosterone, with supplementation advocated for women with total values less than 20 ng/mL (according to her laboratory). She reports that women with low androgen levels have difficulty reaching orgasm, a finding not reported in controlled studies (39). Again, women's ages and pretreatment menopausal status were not discussed in her paper. Clearly, some research is indicated in this area.

Hormonal Therapy for Breast Cancer

Although treatment with antiestrogens is more commonly used for postmenopausal patients, younger women occasionally may be given tamoxifen on an adjuvant basis. More commonly, young breast cancer patients with advanced disease have ovarian ablation by surgery or radiotherapy (41). A variety of hormonal manipulations are given for recurrent disease, including tamoxifen, progestins, aminoglutethimide, luteinizing-hormone-releasing-hormone analogues, and estrogens. Androgens or corticosteroids have also been used as hormonal treatments of metastatic breast cancer, but are viewed as less effective. Adrenalectomy and hypophysectomy have wide-ranging side effects that have reduced their popularity.

Kaplan (32) has the impression from her clinical experience that tamoxifen contributes to vaginal atrophy and may reduce sexual desire by means of decreasing circulating bioavailable androgens. She believes that tamoxifen added to chemotherapy regimens exacerbates their sexual side effects. In fact, a recent review of the impact of tamoxifen on the female genital tract (42) points out that this drug has weak estrogenic effects on the vaginal epithelium. Fornander and colleagues (42) suggest that tamoxifen decreases sex hormone-binding globulins, with the net effect of increasing the bioavailable fraction of androgens. It is important to clarify the impact of tamoxifen on sexual function. If indeed it can prevent vaginal atrophy and increase free androgens, in addition to its positive impact on lipids and bone loss, it could be a safer alternative to estrogen replacement in

young women who undergo premature menopause due to breast cancer therapy.

Little is known about the impact of other hormonal agents on sexual function. Aminoglutethimide has been reported to cause severe vaginal atrophy (43). Loss of ovarian function, whether due to oophorectomy, radiotherapy, use of a luteinizing-hormone-releasing-hormone analogue, or the impact of combination chemotherapy, would of course trigger hot flashes, vaginal atrophy, and dryness, and some decrease in serum androgen levels. The use of the term "castration" to describe hormone therapy for premenopausal women should be avoided in patient contact. This word evokes emotionally distressing images of mutilation and defeminization. The reality is difficult enough when presented in more dispassionate language.

Issues for Future Research

Research on quality of life after treatment for breast cancer has been guided by stereotypes. The traditional view of the woman with breast cancer was of a middle-aged or elderly homemaker whose main concern was losing her breast. Having a mastectomy was viewed as the chief morbidity of breast cancer, with profound damage expected to a woman's self-esteem, psychological adjustment, and marital relationship. In fact, recent studies comparing large samples of women with breast cancer to matched control groups undergoing benign breast biopsy, cholecystectomy, or no medical treatment reveal that breast cancer patients do not have more psychiatric problems, marital distress, or sexual dysfunction (44,45). With choices such as limited surgery or breast reconstruction, women worry less about their appearance and more about cancer recurrence and mortality. The greatest damage to sexual pleasure appears to be associated with combination chemotherapy and with the consequences of menopause.

Younger women with breast cancer deserve special research attention. They appear to be a high-risk group for psychological distress (3). A good part of that distress may relate to interference with various goals of women's reproductive years: feeling sexually attractive, having frequent and pleasurable sex, establishing a committed relationship, fulfilling career aspirations, and having children. When a high-risk group has been identified, researchers not only need to characterize their problems, but to devise and evaluate interventions that prevent or ameliorate psychological distress.

Thus, important research questions include the following: How does age influence women's choices about breast conservation and reconstruction? Do treatments that preserve or restore breast appearance confer a greater psychological benefit for younger patients than for older women? What is the impact of combination chemotherapy on premenopausal patients' sexual function? What effects do hormonal therapies have on sexual function in younger women? What are the risks and benefits of treatments to ameliorate sexual dysfunction in women with premature menopause (including estrogen replacement in various forms, tamoxifen, androgen replacement, non-hormonal medications, and sex therapy)? Even within the younger population of women with breast cancer, can we iden-

tify the subgroup at highest risk for emotional distress, and thus in need of early psychological intervention?

Methodological Issues

Methodology in studying quality of life in women with breast cancer has been problematic in general, but research focusing on sexuality has been especially weak. We cannot design effective treatment programs without accurate information on the type and prevalence of sexual and relationship problems in this population.

Sampling Issues

Few published studies have examined the impact of women's age on sexual satisfaction, function, or behavior after treatment for breast cancer. One problem is collecting large enough samples of women in their 20s, 30s, and 40s. This is an area where collaborative studies may be needed. Some larger cancer centers may also have adequate numbers of young patients. Even within the younger group, we need to pay attention to ethnicity. Values and expectations about sexuality differ across subcultures in the United States. African-American, Hispanic, and Asian-American women often have more conservative beliefs about sexual issues and may be less open in responding to questionnaires about sexuality (46-48).

The psychological impact of breast cancer treatment may differ according to a woman's marital status. Women in happy marriages probably cope the most effectively and experience the least disruption of their sex lives. Never married or divorced women have to face the possibility of being rejected by dating partners. Telling a new partner about the history of cancer and allowing him to see physical scars are sources of anguish for many women (49). Thus, unmarried women may constitute a high-risk group, both for psychological distress and for concern about sexuality. Sexual orientation is another variable that has not been studied. An estimated 3% of American women are exclusively homosexual (50). Although this is a small percentage of the population, in 1992 approximately 5400 new cases of breast cancer would be expected among lesbians (51). Their special needs and concerns have been ignored.

Women who have not finished their childbearing are a group with special vulnerabilities. What are the emotional consequences of terminating an early, planned pregnancy in order to initiate treatment when breast cancer is diagnosed? If the mother gives birth to a healthy child, how is the bonding affected if cancer treatment must be initiated immediately afterwards? How do mothers feel about breastfeeding with one breast? Women with positive lymph nodes may be advised not to get pregnant. Adjuvant chemotherapy can leave young women infertile. How do women cope with the double loss of health and fertility? What kinds of psychological support or counseling can help women in these situations? No empirical research has been published on these topics.

Design Issues

Several design issues are crucial in studying younger women with breast cancer. Particularly in studying sexual function, the impact of age should be separated from that of menopausal status. In studies focusing on breast appearance and body image, this is best done by excluding women rendered menopausal by cancer treatment. When studying the impact of systemic treatment on sexual function, age and menopausal status should both be included as independent variables. A 23-year-old woman who becomes prematurely menopausal after chemotherapy may have quite different problems than a 45-year-old woman who was perimenopausal before the same treatment.

Obviously, researchers must also separate the impact of local versus systemic treatments for breast cancer. It may be difficult these days to find a group of young patients who do not receive systemic treatment. If possible, however, it would be useful to examine relationship and sexual effects of local therapies alone for young women with breast cancer. All too often damage to sexual function from premature menopause has been ignored and problems attributed instead to the emotional trauma of breast loss.

Of course, the most useful studies begin assessing psychological and sexual variables soon after the cancer is diagnosed, with several follow-up assessments at standardized intervals. Even if all women in a research protocol receive adjuvant chemotherapy, a longitudinal design allows assessment of sexual function during treatment, at short-term follow-up when menses may not yet have recovered, and at longer-term follow-up when many young patients may have resumed menstruating. Hormonal and behavioral measures could then be used to estimate the roles of estrogen and androgen deficiency versus psychological variables in causing sexual problems.

What are appropriate control groups in studying sexual function in young women with breast cancer? To look at the morbidity of the whole breast cancer experience, women can be compared with a group of healthy women matched to them in age, marital status, number of children, socioeconomic status, and education. Women with breast cancer could also be compared with those with other life-threatening chronic illnesses, such as diabetes or end-stage renal disease, to see whether breast cancer diagnosis and treatment does unique psychosexual damage. Is breast cancer treatment more devastating to young women than treatment for other malignancies? To answer this question, comparison groups of young women with Hodgkins' disease or gynecological cancer could be used (24). It would be best to compare women whose treatment had similar effects in terms of ovarian function, however, so that the special impact of cancer site or localized therapies could be pinpointed.

Perhaps the thorniest problems in studying sexual function are choosing the variables to measure and finding reliable and valid assessment instruments. A thorough study of the impact of cancer treatment on sexual function should measure the frequency of activity; function in the domains of desire, arousal, orgasm, and pain; changes in sexual practices, i.e., breast stimulation, duration of foreplay, types of genital caressing, positions for intercourse; feelings about body appearance and sexual desirability; the quality of the marital relationship; and overall psychological

coping (52). Because of ethical concerns, we cannot observe sexual behavior and so we depend on self-report measures. Unfortunately, there is little consensus in the field on which questionnaires are most useful; whether it is preferable to use paper-and-pencil measures, face-to-face interviews, or phone surveys; how to achieve good test-retest reliability; whether asking the sexual partner to fill out a parallel form is a good reliability check; or even how to conceptualize variables such as body image or sexual desire (53,54). The few data available suggest that behavioral diaries are more accurate than questionnaires that ask for average frequencies of sex (55). Focusing on a specific, recent time period also may enhance the validity of self-reports of sexual behaviors (56,57).

Studies of sexual function in cancer patients have varied in their approaches. Most have restricted assessment to one or two vague items asking about sexual satisfaction or problems. In my own work, I have used individual items from the Sex History Form, a multiple-choice questionnaire about sexual frequency and function (52). These questions have the advantage of being very specific and standardized, with norms from a healthy community sample. They allow the researcher to look at very fine-grained issues, such as the consistency of a woman's orgasmic capacity with self-touch versus noncoital stimulation versus intercourse. The disadvantage is that test-retest reliability and conceptual validity have not been determined for the Sex History Form. Reliability is usually enhanced by using questionnaires with several items that form a scale, for example, measuring sexual desire. This approach has been taken by Andersen et al. (58) in a longitudinal study of gynecological cancer patients. The disadvantage of her scales is that they may be too general to detect the very specific deficits in sexual function produced by premature menopause or genital surgery. In choosing an assessment instrument, the researcher should consider the question being asked. To find out whether young women with breast cancer have poorer sexual satisfaction than a matched control group, a scale measuring general aspects of sexual function is superior. To pinpoint specific sexual side effects of a cancer treatment, more aspects of sexual function need to be assessed.

With the welcome recent focus on women's health issues at the National Institutes of Health, as well as the end of an administration that singled out sex research for government interference, the outlook is brighter that researchers will be able to obtain support for studies of these important aspects of quality of life in young women treated for breast cancer.

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Breast Cancer in Younger Women: Effects on Interpersonal and Family Relations

Laurel L. Northouse*

Although breast cancer can have a stressful impact on women of all ages, young women may be particularly vulnerable to the negative effects of the disease. Based on a developmental perspective, this article reviews studies on the emotional impact of breast cancer on young women, their spouses, children, and the marital relationship. Studies indicate that younger women experience more emotional distress than older women, although the inverse relationship between age and emotional distress is not consistent across all studies. Although age does not appear to have a direct relationship to husbands' adjustments, younger husbands reported more problems carrying out domestic roles and a greater number of life stresses than older husbands. Studies on the impact of breast cancer on children are limited in number and scope but indicate that the effects of breast cancer vary according to the developmental level of the child. Directions for further research on young women and their families are suggested. [Monogr Natl Cancer Inst 16:183-190, 1994]

Although breast cancer has a stressful impact on women of all ages, there is a growing concern that young women with breast cancer and their family members may be particularly vulnerable to the negative effects of illness. However, little research has addressed the concerns or the impact of the illness on younger women's lives and the lives of their family members. Utilizing a developmental perspective, this article describes the emotional impact of breast cancer on young women, their spouses, children, and the marital relationship; it concludes with directions for future research.

A Developmental Perspective

According to family theorists, families move through different phases over the life cycle of the family (1). These developmental phases are often delineated according to the ages of children and the concurrent changes that families encounter. Olson et al. (1) have identified seven stages of the family life cycle: 1) young couples without children, 2) families with preschoolers, 3) families with school-age children, 4) families with adolescents, 5) launching families (children 19 years and older), 6) empty nest families, and 7) families in retirement. During each of these stages, families face normative demands that are typical of the specific family stage. For example, families of preschoolers face the increased demands associated with the

care of young children, families of school-age children experience the added demands of children's outside activities and sibling conflicts, and families of adolescents face greater intrafamily conflicts. Olson et al. (1) examined the amount of stress and family strain encountered by normal families ($n = 1110$) at different stages. They found persistent levels of family strain during the early stages of the family life cycle that peaked during the adolescent and launching phases and dropped precipitously when families reached the empty nest and retirement phases.

When breast cancer is diagnosed, the demands of the illness are superimposed on the normal demands of family life. When breast cancer occurs in young women, the demands on family life are heightened as family members attempt to cope simultaneously with the day-to-day care of young children and with emerging careers as well as with the added worries of a life-threatening diagnosis, body-altering surgery, and the toxic effects of radiation and chemotherapy. Family theorists contend that when families face an excessive number of demands, a "pile-up" of stress occurs and the well-being of family members and family life is threatened (2). Although family theory suggests that young families are vulnerable to the overload of multiple stressors, researchers have found that there is considerable variability in families' responses to stress. Some families are able to manage multiple stressors with minimal disruption, while other families are overwhelmed and experience considerable distress and many family problems. Researchers are finding that mediating factors, such as the number of family resources and type of family coping strategies, can influence the impact of multiple stressors on families (1).

Emotional Impact of Breast Cancer on Younger Women

Very few studies have looked specifically at the emotional impact of breast cancer on younger women. Of the studies that have examined the relationship between age and adjustment to breast cancer (Table 1), several studies indicate that younger women experience more emotional distress than older women (3-8). However, the inverse relationship between age and emotional adjustment is not consistent across all studies. There have been a number of investigators who have found no relationship

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See "Note" section following "References."

Table 1. Studies that examined age and adjustment to breast cancer

Investigator(s) (ref. No.)	No. of subjects	Design	Measures	Major findings
Jamison et al. (3)	41 breast cancer patients	Descriptive, exploratory	Locke-Wallace marital adjustment test; Rotter internal-external locus of control scale; Eysenck personality inventory; Researcher-designed questionnaire	Women in the younger age group (<45 y) rated their post-mastectomy adjustment as poorer, perceived the mastectomy as having a more negative effect on their sexual relationships, and sought psychiatric help more often than older post-mastectomy women (≥45 y)
Vinokur et al. (4)	274 breast cancer patients	Longitudinal (interviews were conducted at 4 and 10 mo postdiagnosis)	Used a series of items and subscales from Hopkins symptom checklist; Andrews and Whitey quality of life scale; Bradburn's positive affect scale, etc., to measure emotional adjustment; used items from the Framingham disability study to measure physical adjustment	Younger women perceived breast cancer as a greater threat and reported poorer mental health than older women; physical impairments had a more adverse effect on the mental health of younger women than older women
Vinokur et al. (5)	173 breast cancer patients and 176 women without breast cancer who were matched controls	Exploratory, comparative	Several indexes developed from items drawn from the Hopkins symptom checklist; Andrew's and Whitey's quality of life scale; Bradburn's positive affect scale; Caplan's social role function scale, etc.	Interaction effects were found between age and recency of the breast cancer diagnosis and between age and disease severity; a recent cancer diagnosis had a more negative impact on the mental health of younger than older women; advanced disease had a more negative impact on the physical health of older versus younger women
Penman et al. (6)	1715 women who had either mastectomy (661), cholecystectomy (350), benign breast disease (365), or no surgery (339)	Cross-sectional and longitudinal (a subset of the sample was interviewed at 3, 6, 9, and 12 mo postsurgery)	Numerous scales and subscales were used to assess predictor and outcome variables such as: Rosenberg self-esteem scale; Schain feminine self-image and intimacy checklist; sickness impact profile; Ware social health index; Holmes and Rahe social readjustment rating scale; perceived social support scale; Levenson locus of control scale, etc.	Women in the younger age groups (i.e., 30-39) reported lower self-esteem and more concerns about feminine self-image and intimacy; younger women also reported more family dysfunction and life stress than older women
Northouse and Swain (7)	50 breast cancer patients and spouses	Longitudinal (interviews conducted 3 and 30 days postsurgery)	Affects balance scale; brief symptom inventory; psychosocial adjustment to illness scale	Younger women reported more distress than older women just after surgery; 30 days after surgery, age was not related to women's adjustments
Mor (8)	698 colon cancer patients, 150 breast cancer patients receiving active treatment, and 372 breast cancer patients receiving home care	Secondary analyses of the relationship between age and quality of life in three samples of cancer patients	Instruments used varied across samples, but included Spitzer quality of life index; mental health inventory; POMS; CES-D; Karnofsky performance status scale; and other researcher-developed scales	For the most part, age was not related to quality of life across samples; however, in the breast cancer samples, younger women reported more depression and more disruption associated with the cancer than older women
Baider and Kaplan De-Nour (9)	62 breast cancer patients and their husbands	Exploratory	Beck depression inventory; Spielberger anxiety scale; psychosocial adjustment to illness scale; Shanan sentence completion technique; Moos family environment scale	Age had little influence on adjustment, even though a positive significant relationship was found between age problems with sexual relations
Ganz et al. (10)	229 breast cancer patients	Longitudinal (but only baseline data reported in this article)	Functional living index-cancer, cares rehabilitation evaluation system; Karnofsky performance status; profile of mood states; global adjustment to illness scale	Age was not related to women's emotional distress, quality of life, functional status, or global adjustment; age was only weakly correlated with number of rehabilitation problems with younger women reporting more problems than older women
Maunsell et al. (11)	205 breast cancer patients	Longitudinal (interviews at 3 and 18 mo postsurgery)	Life experiences survey; diagnostic interview schedule; psychiatric symptom index	Age had little or no relationship to women's psychological distress
Goldberg et al. (12)	166 breast cancer patients and 156 benign breast disease patients	Longitudinal (interviews were conducted preoperatively and at 6 and 12 mo postoperatively)	Rotterdam symptom checklist	Age was not related to adjustment

between age and adjustment to breast cancer (9-12). This review will focus specifically on those studies in which age was significantly related to adjustment.

In one of the early studies on adjustment to breast cancer, Jamison et al. (3) found younger women (i.e., <45 years old) rated their postmastectomy adjustment as significantly poorer than older women (i.e., ≥45 years). They also found that younger women sought professional help more often and perceived the mastectomy as having a more negative influence on their sexual relationships than did older women.

Vinokur et al. (4) assessed the process of recovery from breast cancer in younger and older women during the first year following surgery, and they found that younger women perceived breast cancer as a much greater threat than older women. Although age was inversely related to women's mental health, the magnitude of the relationship was small. In other words, age accounted for some but not all the variance in women's adjustments. Among those women who reported physical impairments associated with the breast cancer, such as difficulties with lifting and doing household chores, the impact was much greater on the mental health of younger women. Younger women with physical limitations had significantly poorer mental health and a lower sense of well-being than older women.

Vinokur et al. (5) also found age differences when they examined women's long-term adjustment to breast cancer. In this study, younger women with a recent diagnosis of breast cancer (i.e., <5 years) experienced significantly poorer mental health than older women with a recent diagnosis. On the other hand, older women with advanced disease experienced greater physical limitations than younger women with advanced disease. Based on this study and the previous one, the investigators reported that younger women are more vulnerable to the emotional impact of breast cancer, while older women are more vulnerable to the physical impact of breast cancer (4).

Penman et al. (6) examined the impact of a mastectomy on self-concept and social function of women with breast cancer and compared them to women who had benign breast disease, or a cholecystectomy, or no operative disease at all. To determine whether there was a differential response according to age, women were accrued in the study by age groups, 30-39, 40-49, 50-59, and 60-69. Although the three most powerful predictors of women's adjustments were their levels of perceived support, present life stressors, and locus of control, age was related to a number of the psychosocial variables. Younger women reported more problems than older women in areas related to self-esteem, feminine self-image, intimacy, family interaction, and present life stress. No age effect was found in body image dissatisfaction, social health, or social role impairment.

Other studies have also reported an inverse relationship between age and adjustment to breast cancer. Northouse and Swain (7) interviewed newly diagnosed breast cancer patients in the hospital and 30 days later and found that younger women reported significantly more distress than the older women at the time of hospitalization. Thirty days later, however, age was not significantly related to women's emotional distress. Multivariate analyses indicated that other factors, such as women's levels of support, were more powerful predictors of women's distress than age was. Mor (8), studying age and stage of disease dif-

ferences among breast cancer patients undergoing active treatment, found that younger patients were more depressed than older patients, regardless of whether they had regional or metastatic disease. Mor also found that younger breast cancer patients reported higher levels of disruption associated with the disease and its treatment than did older patients.

The preliminary findings of an ongoing, longitudinal study of a couple's adjustment to breast cancer (13) indicate that age is significantly related to a number of psychosocial factors at the time of diagnosis. Couples were interviewed at four times over the course of 1 year: 1) before breast biopsy, 2) a few days after biopsy but prior to subsequent breast surgery, 3) 60 days after surgery, and 4) 1 year after surgery. Three hundred women and a majority of husbands entered the study before biopsy; 86 women were diagnosed with breast cancer. At the time of diagnosis, age was inversely related to breast cancer patients' concern about breast cancer ($r = -.37$; $P < .001$), emotional distress ($r = -.29$; $P < .01$), psychosocial role problems ($r = .23$; $P < .02$), and concurrent stress ($r = -.39$; $P < .001$). Younger women reported higher levels of concern about the breast cancer, more emotional distress, more psychosocial role problems, especially in the domestic area, and a greater number of other life stresses than older women.

There have been few qualitative studies on women's adjustment to breast cancer and as a result little understanding of the concerns of younger women following a breast cancer diagnosis. In one qualitative study (14), newly diagnosed breast cancer patients and their partners were asked to describe their greatest concerns about the illness. The majority of women reported that survival was their greatest concern. Younger women, however, reported that families and children were their greatest concern. Typically, younger women with small children at home worried about whether or not they would live long enough to see their children grow up. A 31-year-old woman made the following comments: "The hardest part for me has not been the mastectomy; that has barely affected me at all. The hardest part is that I have two small children, and I really want to see them grow up. My son is five and my daughter is two, and I want to be there for them. I know that I'm not guaranteed 10 or 15 years but I keep finding myself praying, 'Please God, give me more time'. . . . We've been trying to have a baby for the past 9 months, and I now realize that will not be possible. I feel like a lot is being thrown at me at one time."

This woman's comments and the research suggest that young women may have special concerns about their children and families that need to be taken into consideration.

Although the research is limited, there is some indication that younger women may be at greater risk of more emotional distress following a breast cancer diagnosis. Quantitative studies suggest that the magnitude of the relationship between age and distress ranges from weak to moderate. However, age alone is seldom the most powerful predictor of women's adjustment to breast cancer.

Emotional Impact of Breast Cancer on Spouses

Over the past 15 years, there have been a small group of studies examining the impact of breast cancer on the husbands

of breast cancer patients (7,9,15-19). The consensus of these studies is that breast cancer can have a stressful impact on the emotional well-being of spouses. Husbands of breast cancer patients have reported psychosomatic problems, such as eating disorders and sleep disturbances, following their wives' breast surgery (15), distress levels that are comparable to the levels reported by their wives (7), and feelings of heightened anxiety and depression, starting at the time of diagnosis and continuing through the first year after surgery (16). Some investigators have found that the number of adjustment problems reported by husbands is significantly related to the number of adjustment problems reported by their wives (9), suggesting that health professionals need to focus more broadly on couples at risk rather than more narrowly on individuals at risk.

Husbands of all ages report that one of the most difficult aspects of the breast cancer experience is helping their wives to deal with the emotional impact of the illness (18,20,21). In a study by Zahlis and Shands (18), husbands reported that they often felt unprepared for the intense emotional upheaval experienced by their wives. Although they tried to support, console, and understand their wives, husbands often felt inadequate and unprepared for dealing with their wives' emotional concerns. Sabo et al. (17) found that some husbands attempted to cope with the emotional impact of breast cancer by assuming a protective or guardian role toward their wives. These husbands pushed their emotional concerns to the background and tried to maintain a brave front around their wives. Over time, however, the guardian role took its emotional toll on husbands and their marital relationships. As husbands tried to maintain their facades, they experienced increased moodiness, loss of energy, and gnawing fears about their own health and death. In addition, the protective stance hindered communication between husbands and wives about important issues such as breast loss, sexual adjustment, and mortality.

Although breast cancer has a stressful impact on husbands in general, we know very little about its specific impact on husbands of young women with breast cancer. For the most part, studies conducted with husbands of breast cancer patients either have not examined the relationship between age and spouse adjustment or have not reported their findings in published research reports. The few studies that have been conducted with husbands of younger breast cancer patients or that have examined age in relation to spouses' adjustment to breast cancer are listed in Table 2.

Baider and Kaplan De-Nour (9) conducted one of the few studies examining age and the adjustment of husbands to breast cancer, and they found that age was not significantly related to husbands' adjustments. Northouse and Swain (7) also found no significant relationship between age and adjustment of husbands at the time of their wives' hospitalizations for breast surgery or 1 month after discharge. The strongest predictor of husbands' distress during these times was the husbands' levels of social support rather than their age (22). At follow-up interviews conducted 18 months later, Northouse (23) found that younger husbands reported significantly less positive moods than older husbands; however, this finding was not evident on other measures of adjustment assessed at the time.

Preliminary results from an ongoing, longitudinal study of couples' adjustment to breast cancer (13), discussed earlier, indicated that age was not related to husbands' levels of emotional distress at the time of diagnosis. Age of husbands, however, was inversely related to their adjustment problems in the domestic area ($r = -.45$; $P < .001$) and to the number of other life stressors they were experiencing ($r = -.29$; $P < .01$). Consistent with family theory, younger husbands of breast cancer patients reported significantly more problems carrying out domestic roles, and they were also dealing with more concurrent stresses in their lives at the time of diagnosis than were older husbands.

Table 2. Studies that examined age and spouse adjustment to breast cancer

Investigator(s) (ref. No.)	No. of subjects	Design	Measure	Major findings
Baider and Kaplan-DeNour (9)	62 breast cancer patients and husbands	Exploratory	Beck depression inventory; Spielberger anxiety scale; psychosocial adjustment to illness scale; Shanan sentence completion technique; Moos family environment scale	Age was not related to husband's scores on the adjustment measures
Northouse and Swain (7)	50 breast cancer patients and husbands	Longitudinal (interviews were conducted at 3 and 30 days postsurgery)	Affects balance scale; brief symptom inventory; psychosocial adjustment to illness scale	Age was not related to husband's scores on the measures of adjustment
Northouse (23)	41 breast cancer patients and husbands	Longitudinal (18-mo follow-up interviews)	Affects balance scale; brief symptom inventory; psychosocial adjustment to illness scale	At 18 mo postsurgery, younger husbands reported less positive moods than older husbands; age was not related to the other measures of adjustment
Lewis et al. (19)	48 fathers of school-age children, whose wife had either breast cancer (19), diabetes (13), or fibrocystic disease (16)	Longitudinal (interviews conducted every 4 mo over 18-mo period; time 2 data reported in this article)	Demand of illness inventory; Spanier dyadic adjustment scale; family peer relationship questionnaire; F-Copes scale; CES-D; FACES II	Two factors that affected husband's adjustment were the type of disease his wife had and the number of demands of illness the husband experienced; husbands who reported more illness-related demands also had higher levels of depression

Lewis et al. (19) conducted one of the few studies examining the impact of chronic illness on younger spouses with school-age children. The sample of husbands, averaging 39.5 years in age, consisted of husbands of women with one of three types of disease: breast cancer, diabetes, or benign breast disease. The investigators found that spouses who reported a higher number of illness-related demands reported higher levels of depression. Furthermore, spouses with higher levels of depression reported significantly lower levels of marital satisfaction. One surprising finding in this study was that spouses of women with breast cancer reported better marital adjustments than did spouses of women with diabetes or benign breast disease. The investigators contend that one reason for this difference is that husbands of women with breast cancer developed more elaborate explanations of their wives' behaviors and emotions associated with the effects of the illness than did husbands of women with diabetes or benign breast disease.

Based on the limited number of studies with spouses of breast cancer patients, it appears that age alone is not directly related to husbands' levels of distress. Other factors such as the number of demands that the illness places on younger husbands, the difficulties they encounter carrying out domestic roles, the other life stresses they are dealing with, and their perceived levels of support are better predictors of their adjustments to their wives' illness.

Impact of Breast Cancer on Children

Studies on impact of the mother's breast cancer on her children have emerged only within the past 10 years (Table 3). For many years, breast cancer was perceived as a disease of older women whose children are grown. As a result, the impact

of illness on children was considered minimal, and little research was conducted in the area. It is only in recent years that research on the impact of cancer on the family has emerged (24-26), drawing attention to the needs of all family members following a cancer diagnosis and especially to the impact of the illness on children (27-30).

The limited research in this area indicates that children, like their parents, are not immune to the stressful effects of the illness (27-30). Lewis et al. (27) examined the impact of a mother's breast cancer on children in three developmental stages: young school-age (7-10 years), older school-age (10-13 years), and adolescent (14-19 years). In keeping with a developmental framework, the investigators found differences in children's concerns depending on developmental stage. Younger school-aged children worried about the safety of their family and the ability of their family to stay together. Older school-aged children worried about the disruption that the illness caused in the family and the added household chores that they had to assume. Adolescents struggled with their desires to be independent from parents, and at the same time, they felt responsible for staying near and assisting their parents. Lewis et al. (19) also found that the adjustment levels of the children were affected by the marital adjustment of the parents and by the quality of the parent-child relationship.

Research by Lichtman et al. (30) indicates that adolescents, especially adolescent daughters, may be at special risk when their mothers are diagnosed with breast cancer. The investigators found that breast cancer patients reported significantly more relationship problems with their daughters than with their sons. The problems with daughters were more intense and were characterized by more defensiveness, argumentativeness, and emotional distance. Among possible reasons for the increased

Table 3. Studies on the impact of breast cancer on children

Investigator(s) (ref. No.)	No. of subjects	Design	Measures	Major findings
Lewis et al. (27)	126 families of women with breast cancer who had school-age children	Longitudinal	Demands of illness inventory; child's perception of mother's illness	Children's concerns varied according to their developmental level
Lichtman et al. (30)	78 breast cancer patients, 68 of whom had children; mothers reported on their children's adjustment	Descriptive, exploratory	Several standardized measures were used to assess women's adjustment (e.g., profile of mood states, index of well being); data about children were obtained using a researcher-designed questionnaire	The majority of women (46%) reported no changes in their relationship with their children since the diagnosis of breast cancer; deterioration in mother-child relationship was associated with mothers who had poorer prognoses, poorer adjustments, and more extensive surgery
Wellisch et al. (28)	60 daughters of breast cancer patients and 60 daughters of women without breast cancer (matched comparisons)	Cross-sectional, comparative	Brief symptom inventory; Derogatis sexual functioning inventory; global sexual satisfaction index; sexual arousability inventory; ways of coping checklist	There were no differences between the groups of adult daughters on most of the major study variables; daughters of breast cancer patients reported more problems in the psychosexual area of adjustment than did the comparison group of adult daughters
Wellisch et al. (29)	60 adult daughters of women with breast cancer	Descriptive, exploratory	Brief symptom inventory; Derogatis sexual functioning inventory; sexual arousal inventory; ways of coping checklist	Women who were adolescents when their mothers were diagnosed with breast cancer had more adjustment problems and greater discomfort with their mother's illness than did women who were either adult or younger children at the time of diagnosis

difficulty with daughters were their fears about inheriting the disease, the mother-daughter rivalry, and the high degree of support that some mothers may have expected from them (30,31). Although the problems were more intense with adolescent daughters, the majority of breast cancer patients reported that the illness did not have a detrimental impact on their relationships with their children. Problems with children were more common when mothers had poorer prognoses, more extensive surgery, and poorer psychosocial adjustments.

Recent research has examined whether the impact of breast cancer persists for an extended period of time and affects the psychosocial functioning of adult daughters of breast cancer patients. Wellisch et al. (28) compared the adjustment of daughters of women with breast cancer with a group of women without a maternal history of breast cancer, who were matched on age, education, and race. The investigators found no differences between the two groups of adult women (mean age, 42 years) on psychological symptoms, body image ratings, coping styles, or breast cancer screening practices. However, a few differences were evident in the psychosexual area, where daughters of breast cancer patients reported lower sexual satisfaction and less frequent sexual intercourse than the comparison group of women. The investigators contend that the sexual area may be the area in which adult daughters of breast cancer patients most closely identified with their mothers and hence are most vulnerable to the effects of the illness. The investigators also found differences in daughters' reactions, depending on the daughters' age when their mothers were diagnosed (29). Women who were adolescents at the time of diagnosis reported significantly more emotional discomfort with their mothers' illness than did those who were younger or adults at the time of diagnosis. For the most part, however, the investigators found that adult daughters of women with breast cancer adjusted well over time to their mothers' illness.

Impact of Breast Cancer on Marital Relationships

One of the early myths about breast cancer was that it led to severe marital problems and divorce for many couples. We now know that this is not the case and that couples coping with breast cancer are no more likely to end their marriages than are couples from the normal population (Table 4). Lichtman et al. (32) studied the marital adjustment of breast cancer patients and their significant others and found that the quality of the marital relationship stayed the same or improved after the mastectomy. Only 7% of the couples divorced, and only in two of these cases was the separation due to the impact of the breast cancer (33). In a longitudinal study of breast cancer patients and their husbands, Northouse (23) found that only two couples (4%) divorced over the 18-month assessment time; in both cases, the couples reported that they had marital problems before the onset of breast cancer. Morris et al. (34) found that the marital adjustment of many breast cancer patients in their study remained the same in the 2-year period following the mastectomy. The level of marital adjustment reported by the breast cancer patients was similar to that reported by women with benign breast disease. Carter et al. (35) interviewed a small sample of couples and found a high degree of cohesion, similar to enmeshment, 2-3 years following the mastectomy. The investigators contend that their tendency toward more extreme degrees of cohesion may reflect an adaptive reaction to the threat of breast cancer.

Lewis and Hammond (36) conducted a longitudinal study to determine whether changes occurred in the marital and family adjustment of women with breast cancer who had either school age or adolescent children living at home. Women entered the study approximately 2 years after diagnosis and were interviewed three times over an 8-month period. The investigators found that women's levels of marital adjustment improved significantly over time, and the demands of illness decreased over

Table 4. Studies on the impact of breast cancer in marital relations

Investigator(s) (ref. No.)	No. of subjects	Designs	Measures	Major findings
Lichtman et al. (32)	78 breast cancer patients and their significant others (62)	Exploratory	Profile of mood states; Locke-Wallace marital adjustment test; index of well-being; global adjustment to illness scale; researcher-designed interview	Couples' marital satisfaction was generally high and within normal range following the diagnosis and treatment of breast cancer; younger couples reported higher marital satisfaction than older couples
Lewis and Hammond (36)	111 breast cancer patients	Longitudinal (interviews conducted on 3 occasions at 4-mo intervals)	Demands of illness scale; CES-D; Spanier dyadic adjustment scale; F-COPES; FACES-II	Marital adjustment significantly increased over time; however, if a woman was depressed, her negative mood had an adverse effect on the couple's marital relationship over time
Morris et al. (34)	69 breast cancer patients and 91 benign breast disease patients	Longitudinal (interviews conducted preoperatively and at 3, 12, and 24 mo postsurgery)	Hamilton rating scale; Eysenck personality inventory; researcher-designed questionnaires	Marital adjustment was generally not affected by the mastectomy over time; however, a decrease in sexual satisfaction was reported by 18% of the cancer patients and by 6% of the benign breast disease patients at 3 mo postsurgery
Carter et al. (35)	41 breast cancer patients and their husbands	Exploratory	SCL-90; psychosocial adjustment to illness scale; Dyadic adjustment scale; subscales of FACES III; clinical rating scale	Marital interaction between women and their husbands was characterized by high levels of cohesion, possibly indicative of an adaptive reaction to a life-threatening illness

time. However, there was no change in the level of household functioning. The investigators found that women who were depressed at the start of the study continued to be depressed over the 8 months. Women's depression had a negative effect on their marital relationships and eventually on household functioning.

Although, in most instances, the quality of the marital relationship after breast cancer remains the same or improves, partners often report various marital strains: for instance, in a couple's sexual relationship (34). The incidence of sexual problems reported by couples following a breast cancer diagnosis varies from one study to another, but estimates indicate that approximately one fourth to one third of the couples experience difficulties in this area (15,16,33). Couples at greater risk of sexual problems are those with sexual problems existing before breast cancer. Other difficulties stem from women who have a high emotional investment in their breasts and from husbands who experience a loss of sexual energy because they fear hurting their wives during intercourse (15,37,38).

A second area of strain for couples centers on problems of communicating about the illness. Lichtman et al. (32) found that mastectomy patients had a greater need than their husbands to discuss fears about breast cancer, especially recurrence. Husbands seldom wanted to discuss fears because they thought that talking about fears would create negative emotions and either hinder their wives' adjustments or cause a recurrence. However, couples who were able to maintain open communication reported better marital adjustments following breast cancer. Spiegel et al. (39) found that although many women with advanced breast cancer in their study said that they were able to discuss their illness with their family members (74%), fewer were able to openly discuss their fears (57%). Nevertheless, these women perceived their families as a strong source of support and reported very little conflict.

There has been little research that has specifically examined the impact of breast cancer on the marriages of younger couples or on couples who have been married for a shorter period of time. Northouse and Swain (7) found that women who had been married for shorter periods or who had been married previously (i.e., were in their second or third marriages) reported significantly more distress when hospitalized than couples married for a longer period or couples who were still in their first marriage. Lichtman (33), however, did not find a significant relationship between length of marriage and adjustment. They found a significant relationship between age and marital adjustment. Younger breast cancer patients and their partners reported higher marital satisfaction than older breast cancer patients and their partners (32). More research is needed specifically addressing the developmental stage of the marriage and its role in adjustment to breast cancer. Given the importance attributed to the quality of the marital relationship, it is likely that the quality rather than the quantity of years married will be the stronger predictor of adjustment.

Directions for Future Research

Based on the review of existing research, there are a number of areas in which research is needed. First, there is a need for longitudinal studies of the adjustment of young women and their

partners to breast cancer. These studies need to follow couples from the diagnosis through the first year following surgery, using control group comparisons so that the stress associated with breast cancer can be separated from the normal stress experienced by this age group. Where possible, investigators need to use similar, standardized measures of adjustment or psychological distress [such as the psychosocial adjustment to illness scale (PAIS) (40), profile of mood states (POMS) (41), or brief symptom inventory (BSI) (42)], so that comparisons of couples' adjustments can be made across samples. There also needs to be some consensus among investigators about what age is considered young. In one study, younger breast cancer patients were categorized as women 64 years of age or less (5), whereas in another study younger breast cancer patients were categorized as women who were less than 45 years of age (3). The approach of Penman et al. (6) to categorizing women's ages by decade (e.g., 30-39, 40-49) may be a useful approach for examining developmental issues of younger women and their partners but will require access to a large number of breast cancer patients to obtain an adequate number of women in each category. For the most part, we know very little about the needs of young women and their partners, primarily because so few young women have been included in studies that have relied on convenience sampling procedures. Quota or purposive sampling procedures are needed (43), using multiple data collection sites, so that an adequate sample of young women and their partners can be obtained.

Second, there is a need for comparative studies of young, middle-age, and older women and their families who are coping with breast cancer. In a developmental framework, families from the normal population are confronting different issues at various stages. It is likely that the problems that families confront or the fears they experience following a breast cancer diagnosis may also vary significantly from one family stage to another. Studies that examine families' special needs for information, support, communication, or home care assistance, according to the families' developmental stage, will enable health professionals to tailor psychosocial interventions to address the families' specific needs. Studies such as these, however, will require the collaborative efforts of multidisciplinary research teams that are knowledgeable about family and developmental theories. These studies will also require the use of various instruments that are suitable for obtaining data from children, adults, couples, and families.

Third, there is a need for multivariate studies that will identify women, partners, and children who are at greater risk of poor adjustment to breast cancer. Given the variability in individuals' and families' responses to breast cancer, it would be helpful to identify a profile of *young* women and their families who are at greatest emotional risk so that interventions can be targeted directly to this high-risk group. The following factors appear to put breast cancer patients and their family members at risk: having little support from others (22,39), experiencing many illness-related demands (19), having many life-event stresses before diagnosis (11), and being on active treatment for the disease (e.g., chemotherapy) (23,44). In a recent study by Schag et al. (45), breast cancer patients at higher risk of poorer adjustment 1 year after surgery reported more problems communicating with their partner, more interpersonal tensions with family

and friends, more difficulty with body image changes, and more physical problems at the postoperative site. Although further research is needed on factors that place young women and their families at risk, clinicians may want to consider these factors as they plan strategies to assist women and their family members in adjusting to the impact of the illness.

In summary, there is a need for more research on the impact of breast cancer on young women and their family members. We need to find ways to assist young women and their family members to cope with the effects of the illness so that the well-being of all family members and the quality of family life are maintained following the diagnosis of breast cancer.

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Age Differences in the Psychosocial Problems Encountered by Breast Cancer Patients

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Breast cancer afflicts more than 180 000 women in the United States annually (1,2). For women 40-55 years of age, breast cancer is the leading cause of death (3). It has frequently been reported that the diagnosis and treatment of breast cancer produce heightened psychosocial morbidity in a significant number of patients in the form of affective distress, impaired role functioning, disrupted social integration and support, compromised coping, aversive somatic symptoms, unmet practical needs, and increased financial pressures.

Despite the numerous investigations into the psychosocial impact of the diagnosis and treatment of breast cancer, little attention has been focused on how this impact might differ as a function of a woman's age. In large measure, age serves as a marker for the various social roles women play throughout their life span. At younger ages, families are more concerned with the psychological and financial needs of children in the home. Consequently, younger women frequently have dual responsibilities: as "primary caregiver" to their husbands, children, and parents and as "breadwinner," working outside the home to augment the financial resources of the family. Later, the "empty nest" and postretirement periods pose a different set of needs and opportunities for members of the family unit which, in turn, may vary as a function of whether the woman has retained the role of caregiver (4).

Using survey data obtained from breast cancer patients at various stages of the disease process, the goal of this study is to examine the effect of age on women's perceptions of the psychosocial impact of their illness. Specifically, we examine the effect of age at the bivariate level and in multivariate analyses, controlling for potentially confounding factors. Finally, we discuss our findings in light of the contrast between age differences in patients' objective circumstances versus their perceptions of illness impact.

Background

Estimates of the prevalence of psychosocial morbidity among breast cancer patients vary but are consistently higher than for those without cancer. For example, depressive symptoms in cancer patients are twice the level found among general medical patients (20%-74% versus 12%-30%, respectively) (5-8). While a number of factors, including study design, selection procedures, and the measurements used are responsible for the variability in reported prevalence rates, it conservatively appears that between 20% and 25% of diagnosed breast cancer patients experience psychosocial morbidity that persists for at least 1 year after diagnosis (6). For the most part, younger breast cancer

patients report higher levels of emotional distress than do older women with breast cancer (9-13).

Various factors have been associated with elevated psychological morbidity in both prospective and cross-sectional studies. These factors fall into a number of broad categories such as: 1) temporal factors; 2) biological/medical/treatment factors; 3) social support; 4) unmet practical needs; and 5) financial needs due to illness. To date, however, little has been done to explore the relationship of patient age to these factors, particularly when controlling for breast cancer patients' case mix.

Psychosocial morbidity in breast cancer patients varies as a function of time; affective distress is highest immediately following diagnosis. Significant attenuation of distress usually occurs 6-12 months following diagnosis, but distress levels continue to be elevated relative to noncancer comparison groups for up to 5 years (5,8,9,14-17). Of particular interest, younger breast cancer patients experience greater affective distress in the first year following diagnosis and at 5-year follow-up than do those who are older with comparable disease severity, apparently due to the greater fear of recurrence and the presence of competing caregiving demands (9,10,18,19).

Biological, medical, and treatment factors have shown significant associations with the occurrence of psychosocial morbidity. These include stage of disease, type of treatment, and symptoms. More advanced disease stages are associated with more physical problems and emotional distress, including suicidal ideation (17,18,20,21). In addition, types of medical treatment may produce higher rates of psychosocial morbidity in certain areas, with more for adjuvant chemotherapy than for radiation therapy (19).

Since older women are somewhat more likely to be diagnosed with more advanced disease and to report more co-morbid illnesses and impaired physical and cognitive functioning (22-26), one might expect that they would manifest greater levels of psychological morbidity. The little data available exploring the complex relationship between age, extent of disease, symptom severity, treatment modality, and psychosocial morbidity suggest the opposite. To date, studies of older women with breast cancer have reported lower levels of emotional distress than

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their younger counterparts, both earlier in the course of treatment and at 5-year follow-up. Indeed, younger breast cancer patients with more serious physical impairments experienced significantly greater deterioration in their emotional well-being, both during the first year after their diagnosis and at 5-year follow-up than did older women with comparable disease status (9,11).

Social support encompasses the variety of relationships that connect us to our social environment. Most research has found that higher levels of social support attenuate the occurrence of psychosocial morbidity (5,6,27-33). That one type of social support may have a greater impact on adjustment to breast cancer than another, however, is suggested by Primomo et al. (33), who demonstrated that perceived social support was predictive of later adjustment while the size of the social network was not. Despite the perceived importance of social support to emotional well-being, little attention has been focused on whether younger and older patients are differentially affected by various aspects of social support.

Recent research investigating the practical needs of cancer patients and their families (e.g., personal care, meal preparation, child care, shopping, housekeeping, transportation, and financial assistance) indicates that the need for services increases with patient and caregiver age (34-36) and varies during the course of illness (37). As might be expected, higher levels of unmet need for assistance with daily needs were reported by patients with metastatic disease, greater numbers of physical symptoms, and more restricted physical health (19).

Of particular interest, women were more likely than men to report unmet practical needs in the area of instrumental tasks, such as housekeeping and cooking, which tend to be related to their role as primary caregiver in their families (39). However, women over 65 years of age with breast or colon cancer were less likely than younger women to report high levels of unmet instrumental needs (37,38). Older women may have fewer competing demands later in life and, if present, may have partners who are not engaged in full-time employment. Consequently, occasional assistance in shopping or for transportation may be sufficient. Conversely, younger impaired cancer patients, facing multiple responsibilities inherent in life's mid-course, may have younger children who require more assistance than they are able to offer and may also have spouses working full-time to support their families (37,40,41).

There is virtually no literature on the financial impact of breast cancer on older and younger patients and their families. In one study including patients with diverse cancer types, almost 75% of cancer respondents were forced to use savings, and more than half were compelled to apply for financial assistance to meet illness-related expenses (41). No specific studies focusing on breast cancer have been conducted.

Methods

This research is based on data from two studies funded by the National Cancer Institute, whose methods have been described previously (42,43). We included only those patients with breast cancer from each study sample. The two datasets were combined because the data methods and data collected were quite

comparable. Each study is briefly described in the paragraphs that follow.

Nurse Case Manager Trial

Data were derived from the baseline interview of a randomized trial of the impact of short-term nursing case management on the psychosocial needs of patients starting a course of outpatient chemotherapy (43,44). Patients were identified in the private practices of community medical oncologists as well as at two hospital-based medical oncology clinics. After consent was obtained from the patient's physician and the patient, telephone interviews were conducted to characterize the patient's health and social status and measures of psychosocial need. Interviews were supplemented with data from the patient's medical record to document study eligibility.

Home Care Needs of Cancer Patients

This was a multi-site, descriptive study of the home care needs of patients starting a course of chemotherapy or radiation therapy in Rhode Island, rural Pennsylvania, or New York (19,38). Patient interviews were conducted over the telephone after obtaining release from the patients' physicians to allow research staff to contact the patient.

Common Quality of Life Measures

In both studies, the interview contained questions and scales measuring patient's physical and psychosocial quality of life. Those measures that are identical across the two studies are used here to address our research questions among women with breast cancer.

To assess psychosocial status, both studies used the Mental Health Inventory (MHI-5), a five-item scale standardized in medically ill populations (45). A sub-scale of the MOS Short Form General Health Survey (SF-36), the MHI-5 is strongly correlated with much longer general health scales and is able to predict diagnoses of depression (46). A Treatment Impact Scale was developed by study investigators. This scale consists of four items that asked patients about the perceived level of difficulty or disruption that their treatment caused in their daily routine and social functioning.

Both studies used the Activities of Daily Living Index (ADL) and the Instrumental Activities of Daily Living Scale (IADL) (47) as the bases for assessing patients' needs and unmet needs for assistance with daily activities, such as shopping, cooking, etc. Areas of perceived need were assessed in five domains based on their implications for service delivery: personal activities (bathing and dressing); instrumental activities (meal preparation, light housekeeping, shopping); administrative activities (assistance with paperwork, applications for assistance); child-care activities (care for children in the household); and transportation (to the doctor and for general purposes). An indicator of unmet need for assistance was developed based on patients' reports of receiving insufficient help with activities for which help was needed (19,37,38,48).

Measures of the financial impact of illness common to both datasets included respondents' perceptions of how the illness affected their family income and expenses and whether they had

sought outside financial assistance (loans or public aid) or had used savings or other assets to meet their financial needs. In addition, all patients were directly asked if they were experiencing financial problems due to their illness.

Independent variables common to both sets that have previously been found or might be expected to contribute to patients' affective distress, unmet practical needs, financial difficulties, and/or treatment disruptions were included. Encompassing three domains, these were as follows: 1) sociodemographic characteristics, such as patient age, marital status, education level attained, employment status, family income, occupational status, and living arrangements. Racial characteristics (minority versus nonminority status) were not used in analyses due to the small number of minority women in the study population ($n = 20$); 2) social support indicators, such as size and degree of confidence in social support system and children living in the house or near home; and 3) disease and treatment indicators, such as extent of disease and primary treatment modality. Extent of disease was operationalized as a dichotomous variable: local/regional (stage I-IIIa) versus metastatic (stage IIIa/IV). We also asked patients which of 10 different symptoms they had experienced in the last 2 weeks and determined the count of different symptoms reported. Primary medical treatment modality at the time of the study was either chemotherapy or radiation therapy; very few patients were receiving both treatments simultaneously.

Analytic Approach

We conducted bivariate analyses of the relationship between patient's age and each psychosocial outcome. We tested the independent effect of age on each of our outcome variables controlling for the confounding influence of demographic, social, and medical variables, using logistic and multiple regression techniques. Multiple linear regression was used when the dependent variables were continuous (the MHI-5 and the Treatment Impact Scale), and logistic regression techniques were used when the dependent variables were dichotomous (the presence or absence of an unmet need and the experience of financial problems).

In our bivariate analyses, we chose to dichotomize age at over or under 55 for largely practical reasons, since there were sufficient numbers of women with breast cancer over and under this age. Most importantly, we realized that women from 45 to 55 are going through a mid-life transition involving changing roles, demands, and expectations as well as hormonal changes relative to the menopause. However, since these changes in social role and physiology vary in timing, we used age as a continuous variable in all multivariate analyses.

Results

Sample Description

Table 1 describes the older and younger women in the sample on selected independent variables. Although not necessarily representative of the entire population of women with breast cancer, the study population does reflect the sociodemographic make-up of the practices from which patients were recruited. Younger patients were more likely to be married than were

Table 1. Sample description by age

	24-54 y (n = 143)	≥55 y (n = 119)
<i>Demographic and social characteristics</i>		
% married [‡]	67.7	52.9
% with some college [‡]	53.2	20.5
% employed [‡]	51.8	14.3
% family income > \$30 000 [‡]	49.7	17.6
% non-white	10.2	5.4
<i>Social support characteristics</i>		
% living alone [‡]	12.4	27.5
Average No. of people depend on ^{‡,§}	7.6 ± 4.4	6.0 ± 4.3
High degree of confidence in support [‡]	85.5	72.3
Children live nearby [‡]	31.7	62.9
Children live in house [‡]	59.9	28.2
<i>Clinical characteristics</i>		
% local/regional disease [‡]	65.0	38.2
% receiving chemotherapy [*]	80.4	67.2
Average No. of symptoms [§]	2.0 ± 1.3	1.9 ± 1.4
Most common symptoms reported		
Pain	49.6	46.8
Nausea	56.9	49.6
Diarrhea	29.9	22.5

* $P < .05$.

[‡] $P < .001$.

[§] $P < .010$.

§ Values = means ± SD.

older patients (67.8% versus 52.9%). Younger women with breast cancer were also more likely than older women with breast cancer to be employed, to have attended college, and to have family incomes exceeding \$30 000. Younger women were more likely than older women to report children living in their home (59.9% versus 28.2%). Although older women were more likely to live alone, more than 60% reported having children living within a 30-minute drive from home. Younger women reported both larger numbers of people whom they could rely on for help and a higher degree of confidence in their support system than did older women.

Almost two thirds of younger women had regional or local disease versus only around 40% of older women. In keeping with how the samples were selected, 80% of younger and 67% of older women were receiving chemotherapy. Neither the number nor the types of symptoms reported varied by age.

Bivariate Analyses

Emotional well-being. No differences were noted in the composite weighted index (MHI-5) assessing emotional well-being among younger and older women with breast cancer (Table 2). However, significant age differences were found in the two items asking about happiness and the degree of calmness, with nearly 50% of older women describing themselves as "mostly happy" versus only 34% of younger women. Similarly, nearly half of older breast cancer patients reported being "mostly calm" as opposed to only 30% of the younger patients.

Unmet needs. The average number of tasks for which patients needed assistance did not differ by age group (3.9 versus 4.4). However, younger breast cancer patients reported significantly higher numbers of unmet needs across all domains

than did older women (Table 3). Younger women were more likely to have unmet needs in the areas of administrative and child-care tasks. While older women were less likely to report unmet needs in the instrumental task area, this difference did not reach conventional levels of statistical significance.

Treatment disruptions. Following medical treatment, younger women with breast cancer reported having significantly greater difficulty tolerating chemotherapy and maintaining their daily routine (Table 4). No significant differences between age groups were noted in the composite score of the Treatment Impact Scale. There were no significant intergroup differences noted in the patients' ability to maintain outside activities and to continue their usual social activities. However, both groups appeared to have experienced considerable disruptions in their social activities as a consequence of their treatments for cancer.

Financial problems. The economic consequences of breast cancer were reported to be far more pronounced for younger

women than for older women on our subjective measures of financial difficulties (Table 5). Overall, younger breast cancer patients were almost twice as likely as older patients to report having experienced financial problems due to their illness. Specifically, younger women were more vulnerable financially than were older women in terms of lost income and seeking additional monetary help (especially from other family members). However, age was not significantly related to having increased expenses, spending down assets, and borrowing or using savings. Indeed, the proportion of women reporting these problems was fairly prevalent regardless of age.

Multivariate Analyses

Controlling for patients' medical, sociodemographic, and economic factors, the strength of observed bivariate relationships was confirmed in a multivariate analysis. Multivariate linear regression showed that younger age was associated with lower levels of emotional well-being (Table 6). In addition to younger

Table 2. Mental health index (MHI-5) stratified by age

Mental Health Index (MHI-5)	24-54 y (n = 143)	≥55 y (n = 119)
Individual items, %		
Mostly happy*	33.6	49.6
Mostly calm*	30.1	46.2
Mostly nervous	11.9	9.2
Mostly blue	7.7	8.4
Mostly "down in the dumps"	3.5	2.5
Mean composite weighted index (MHI-5) ± SD	67.6 ± 15.3	71.0 ± 16.6

*P<.01.

Table 3. Breast cancer patients' needs for assistance stratified by patient age

Needs and unmet needs for assistance	24-54 y (n = 143)	≥55 y (n = 119)
Average total needs reported*	3.9 ± 2.5	4.4 ± 2.6
Average total unmet needs reported*,†	1.1 ± 1.7	0.6 ± 1.3
Reported unmet needs, %		
Personal needs	4.2	4.2
Administrative needs†	29.4	14.3
Transportation	11.9	7.6
Instrumental	20.1	12.7
Child care‡	5.6	0.0

*Values = means ± SD.

†P<.01.

Table 4. Treatment impact stratified by patient age

Treatment impact	24-54 y (n = 143)	≥55 y (n = 119)
Individual areas of disruption (yes/no)		
Difficulty with chemotherapy	77.6	65.6
Disruption daily routine*	72.7	60.5
Disruption outside contacts	34.3	26.9
Disruption on social activities	61.5	56.3
Treatment Impact Scale score (0-12)†	4.7 ± 3.3	4.0 ± 3.6

*P<.05.

†Values = means ± SD.

Table 5. Financial consequences of breast cancer stratified by age

Financial consequences	24-54 y (n = 143)	≥55 y (n = 119)
Financial problems*	47.4	25.0
Decreased household income*	75.2	52.9
Increased expenses	60.1	50.4
Sold assets	5.9	2.8
Used savings	38.5	38.3
Borrowed money	8.2	4.7
Received financial help from family‡	14.7	4.6
Applied for public assistance‡ (SSDI,§ Medicaid)	32.1	20.9

*P<.001.

†P<.01.

‡P<.05.

§Social Security Disability Income.

Table 6. Regression analyses: factors influencing emotional well-being, needs for assistance, treatment impact, and financial problems

Independent variables	Emotional well-being (continuous)	Unmet needs for assistance (no/yes)	Treatment Impact Scale (continuous)	Financial problems (no/yes)
Age (continuous)	0.417*	-0.053*	0.053†	0.072*
Employed (no/yes)	—	0.012	-0.494	-0.492
Married (no/yes)	5.789‡	-0.157	-0.145	-0.345
Some college (no/yes)	4.825‡	—	1.070†	-0.038
Family income ≥\$0 000	—	—	—	-0.711†
Lives alone (no/yes)	—	1.160†	0.529	—
Confidence in support system (no/yes)	2.905†	-0.694*	-0.921*	—
No. of people could rely on (≤5/6-22)	0.713‡	-0.028	-0.081	-0.062
No. of needs (0-11)	-0.993	0.368*	—	—
Increased expenses (no/yes)	-3.799†	—	—	—
Local/regional disease (no/yes)	—	-0.467	0.450	0.328
Chemotherapy (no/yes)	-1.494	0.160	-0.649	—
No. of symptoms (0-7)	-2.501*	—	—	0.354‡

*P<.001.

†P<.05.

‡P<.01.

age, a number of other factors contributed independently to explain variation in the reported levels of emotional well-being. Lower levels of emotional well-being were associated with being unmarried and having a high school education or less. Not surprisingly, lower levels of emotional well-being were also associated with greater numbers of symptoms and areas of need for assistance. On the other hand, social support factors had a protective effect: i.e., greater numbers of reported helpers and high confidence in the resiliency of social support were associated with higher levels of emotional well-being. Finally, increased cancer-related expenses significantly contributed to lower emotional well-being.

Using the presence or absence of unmet needs in any area as a dichotomous-dependent variable, logistic regression showed an inverse relationship between age and unmet needs, even after controlling for the confounding of selected independent variables. Breast cancer patients living alone, those reporting more total needs, and those reporting less confidence in their social support system were also most likely to report unmet practical needs. Marital status, employment outside the home, extent of disease, type of treatment, and size of social support system were not significant predictors of unmet practical needs for breast cancer patients.

Although being over or under 55 years of age was unrelated to the average Treatment Impact Scale score, after controlling for medical and other support factors, age was significantly inversely related to treatment impact when entered into the regression equation as a continuous variable. Furthermore, low confidence in the social support system and having some college education were associated with higher levels of disruptions (Table 6). Marital status, paid employment, living alone, size of support system, stage of disease, and type of treatment were not significant predictors of the extent to which treatments disrupted daily activities once the perceived resiliency of the social support network was considered.

Controlling for various factors in multivariate analyses did not diminish the significant effect of younger age on financial problems (Table 6). Using the presence or absence of financial problems due to the patient's breast cancer as a dichotomous variable, logistic regression showed that younger age, symptom severity, and higher income were significantly related to financial difficulties. Marital status, employment outside the home, education level, size of support system, and stage of disease were not significant predictors of financial difficulties encountered by breast cancer patients.

Discussion

Our data strongly support our expectations that breast cancer patients manifest age-related differences in the psychosocial impact of their illness. Objectively, younger women are better off in terms of socioeconomic status, social support availability, and extent of disease. Subjectively, however, they experience the effects of their illness more negatively, reporting higher levels of perceived emotional and financial distress, more unmet practical needs, and greater disruptions in their daily lives following medical treatments. Furthermore, these age-related differences

persist even after controlling for disease severity, family income, education, marital status, and social support.

Possible explanations for this apparent contradiction include the following: 1) this is an "off time" event which is, therefore, experienced as more stressful for younger than older women; 2) younger women are generally viewed as the primary caregivers in their households, and hence their own adjustment is complicated by their families' reaction to a sudden change in social role; 3) for this age cohort, younger women are more likely to be in the work force for economic reasons and, as such, also have a "breadwinner role"; and 4) younger women, with both greater familial and financial resources, may feel they have more to lose. We address each of these topics in the paragraphs below.

Previous studies have noted that not only does the prevalence of breast cancer increase with age, so do the expectations of the diagnosis by patients. Older women may view a diagnosis of breast cancer as an expected event, associated with their growing older. For younger women, there is no such expectation (49). Indeed, the initial diagnosis and subsequent treatment are experienced as traumatic events, seriously disrupting daily activities and imposing a premature sense of mortality (50). Families experience similar reactions. The developmental model of family composition and function proposed by Oleson (4) provides a conceptual framework for understanding the disproportionate disruptions experienced by younger breast cancer patients and their families. As the primary caregivers in their families, younger women are frequently more involved in meeting the needs of their partners and their children, whether the latter are still living at home or are "launched" in their young adult roles. The diagnosis of and treatment for breast cancer change these relationships. The primary caregiver is now in need of support from her dependents. For many younger women, the disruption of this key and defining role as primary caregiver is a source of considerable emotional distress. For older women with breast cancer, their role as primary caregiver is more limited, particularly if they are widowed. Families also may be more prepared to provide support rather than to continue receiving support from older parents. Hence, older women may experience less emotional distress and may report fewer unmet needs and treatment disruptions than their younger counterparts (34,36-39).

The role of primary caregiver is not the sole contribution younger women with breast cancer make in their households. They also may be economic providers. Whether their role is primary or secondary to their husbands, younger women are more likely to be employed than are older women, and their income is important to the families' economic well-being. Since their families may still be paying off home mortgages, preparing and educating offspring, and frequently caring for their own parents, the disease is disruptive financially. To the extent that health insurance coverage for the younger woman herself and/or for her family is dependent on her employment, the sense of risk of insurance loss may be high. On the other hand, although older women are frequently on fixed incomes, their fixed expenses may be lower, and they have a more secure source of publicly financed health insurance coverage.

As more women are employed outside the home, their jobs have become a source not only of financial support for their families but also of emotional support for them. Because of the untimeliness of their diagnosis, the jobs occupied by the younger breast cancer patients may be endangered or lost, especially if the patients are receiving daily radiation treatments or experiencing significant side effects from their chemotherapy.

The "relative deprivation" hypothesis would suggest that younger women perceive themselves as having more to lose if their disease progresses. Subjectively, this may be the reality experienced by younger breast cancer patients. Contributing to both patients' perceptions and the realities of their illness are their physicians' attitudes and behaviors. For the most part, physicians share their patients' subjective perception of greater potential loss; consequently, younger women are the recipients of more aggressive treatment protocols (22,24,51).

Our research confirmed earlier efforts regarding the protective role of social support for breast cancer patients (32,33,38). Patients with greater confidence in their social support system, larger social support systems, and not living alone reported less psychosocial distress. Although the mechanism by which social support buffers the impact of the disease experience is not well understood, the uniformity of findings related to its protective effect emphasize the vulnerability of women with fewer social support resources. Similarly, women with fewer economic resources are harder hit by the diagnosis and treatment of cancer, which is consonant with research findings relating low socioeconomic status to a diversity of adverse medical and psychosocial outcomes (5,6,13).

In summary, age-related differences in psychosocial problems appear to be real for women diagnosed with and treated for breast cancer. The greater emotional and financial distress experienced by younger women, coupled with their greater unmet practical needs, presumably reflects the "off-timedness" of their diagnosis, its disruption of their roles as primary caregiver and "breadwinner," and their perception of having more to lose (including their careers and the opportunity to see their children grow and mature). While younger women in our sample appear to have greater financial and psychosocial resources at their disposal, those resources may need to be allocated to a broader array of family goals and may be more easily eroded by the threat to financial security that a chronic disease such as cancer may pose to their families dependent on the income and other benefits that are derived from their employment. Future research in larger, representative samples of older and younger women with breast cancer is needed to confirm these insights and to further disentangle the objective and subjective aspect of the psychosocial consequences of breast cancer.

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Risk and Timing of Counseling and Support Interventions for Younger Women With Breast Cancer

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It is currently estimated that 25% of women have significant anxiety or depressed mood following treatment for breast cancer (1,2), and an equal number report sexual problems (3). A consistent finding across studies is that these problems occur regardless of whether the treatment entails breast conservation or mastectomy (4-7). Thus, while most women cope well with the diagnosis of this life-threatening disease and the stress of breast cancer treatment, a significant minority of women need some assistance during this stressful period. It is presumed that psychosocial intervention can facilitate coping with the disease and potentially improve the quality of life for the majority.

Who is at greatest risk for psychosocial problems following the diagnosis and during the course of treatment of breast cancer? Can intervention improve coping with these "unfair" life circumstances? What types of interventions should be offered? When should interventions be offered? How involved should one's physician be in making referrals? What should be the direction of future research in this area? These questions guided the development of our approach in considering counseling and support interventions for younger women with breast cancer. By younger women, we refer to approximately one third of women diagnosed before menopause with breast cancer. This group of women may be particularly vulnerable to psychosocial morbidity as they are faced with the diagnosis of a life-threatening disease and the body damage resulting from its treatment. At the same time, they are confronting issues of work and careers; finding a mate and becoming a couple or remaining single and, perhaps, living alone; being or becoming a parent, and maybe being a single parent; and the possibility of premature and abrupt menopause. Thus, while we often think of psychosocial interventions following the phases of cancer—diagnosis, treatment, rehabilitation, and continuing care—we must also consider the interactions between phases of treatment and the woman's life stages and role identities.

These questions will be addressed as follows: First, who is at greatest risk for psychosocial problems, and when is the risk greatest? Second, how efficacious are counseling and support interventions in reducing psychosocial morbidity? Finally, what directions for future research result from this review?

Risk and Timing of Interventions

What puts a woman at risk for problems? When and what type of interventions should be offered? Reviews of the literature by Lewis and Bloom (8), Meyerowitz (9), and Glanz and

Lerman (10) suggest a number of factors associated with poorer psychosocial adjustment following a diagnosis of breast cancer. Of the sociodemographic characteristics, age is the most cited. However, the findings are inconsistent as to whether being younger or older puts the women at greater risk. As Glanz and Lerman (10) note, the absence of other demographic factors (e.g., ethnicity or race, education, income, and marital status) may be a function of the homogeneity of study populations (the modal woman in most studies being married, white, about 52, and having two children) more than their lack of importance. Other risk factors include premorbid psychological distress; physical disability; symptoms related to surgery, such as poor wound healing or postsurgical infection; symptoms related to treatment (e.g., alopecia, swelling of arm, and weight gain or weight loss); and stage of disease.

To provide further information and possible validation of these risk factors, we analyzed data from the Psychological Aspects of Breast Cancer Study (PABC) (11), a collaborative study funded by the National Cancer Institute (NCI). The following research questions guided our analyses:

1. When is the woman at the greatest risk for psychosocial morbidity following surgery?
2. What factors in the woman's background, treatment experience, and personal resources put the woman at risk for psychosocial morbidity?

Background

The goal of the PABC was to determine whether the diagnosis and treatment of cancer caused psychosocial morbidity. If such problems resulted from cancer, it was reasoned that, because of its involvement with a sexual organ, such problems would be found among individuals diagnosed with breast cancer. Five investigative teams collected data from 61 hospitals in 11 states to examine this question. The total study included both cross-sectional ($n = 1701$) and a longitudinal ($n = 412$) samples. For the cross-sectional sample, data were collected for five groups 0-3, 3-6, 6-9, 9-12, and 12-15 months after surgery; for the longitudinal sample (women first entered the study from 2

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See "Notes" section following "References."

weeks to 3 months after surgery), data were collected at 3-month intervals over the course of 1 year. Women were selected whose breast cancer was either stage I or stage II and were between 30 and 70 years of age. The sample was selected so that the size of the sample would be relatively similar by stage and by age (age groups were 30-39, 40-49, 50-59, and 60-69). Comparison groups were selected that had onset patterns and prevalence similar to breast cancer (found in ages 30-70), yet separated the psychosexual and life threat of breast cancer from the effects of major surgery (gallbladder disease and benign biopsy). A healthy, nonsurgical comparison group was also selected.

The use of these data provides the opportunity to examine the risk and timing of psychosocial distress on a large sample of younger women with breast cancer. To address these issues, the cross-sectional sample is used for only the breast surgery and healthy groups.

Sample

The sample for these analyses consists of 948 women, 661 of whom had a mastectomy for stage I and stage II breast cancers; the remainder form a nonsurgical comparison group. More than a third of the sample are "younger women" as the sample was stratified by age, 10.4% of the sample were between 30 and 39, another 24.4% were between 40 and 49, and the remainder were between 50 and 59 or between 60 and 69. Most of the sample (66.5%) were married, 12.8% were widowed, 13.6% were separated or divorced, and 7.2% were single. The average number of children was 2.2. Slightly fewer women with breast cancer never had children (18% compared with 20%). Of more relevance to this analysis is the number of children living at home; less than a third of the sample had children under 21 years of age living in the household (32%). Among the cancer sample, 34.6% had adjuvant therapy in addition to a mastectomy; none had breast-conserving treatment (Table 1). An important feature of the sample is the physical and psychological health of the women. Women who had received any type of counseling, including marital counseling or psychotherapy within 2 years of breast surgery, who were taking psychotropic medications, or who had a disabling physical condition (Karnofsky performance status less than 70) were excluded from the sample. Another feature is that all of the sample had a mastectomy; none of the sample had breast-conserving treatment. However, literature comparing these two procedures indicates that only body image differentiates them—women who had a mastectomy have a lower body image score than those who had breast-conserving treatment (2).

Measurement

We selected measures that in the research literature have been cited as risk factors for psychosocial morbidity (Table 2). These measures include demographic factors such as age, time since surgery, marital status, employment status, having young children at home, and socioeconomic status (12). A second set of factors was health related, such as having adjuvant therapy as part of the treatment regimen, experiencing side effects of treatment (e.g., alopecia, swelling of the arms, weight gain or loss, and slow wound healing), health status (including perceptions of

health, days in bed, and activity reductions) (13), physical functioning (e.g., walking a half mile, walking up stairs, and carrying groceries), and the amount of change occurring in one's life (14).

If the factors described above are risk factors for psychological morbidity, then social and emotional support from family and friends may provide a natural intervention. This assumption is based on literature from a number of studies inversely linking depression and anxiety to social support (15,16). Three measures of social and emotional support are included: perceptions of emotional support (17), family support (18), and social connections (19). One's self-esteem as a measure of personality strength is also included (20).

Our measures of psychosocial morbidity are two self-report measures from the Brief Symptom Inventory (21). The two measures are the depression scale and the Global Severity Index, which is the most sensitive global measure of the scale indicating depth of morbidity.

Analysis

We developed two models for analyzing these data using multiple regression. In the first analysis, we assessed the effect of time on psychological response. We included women who had cancer, as the time dimension only has relevance for this group of women (Table 3). In the second analysis, we assessed the effect of the women's sociodemographic background, health factors presumably associated with their risk for poorer adaptation, and measures of their personal and social resources. These analyses included the sample of healthy women as well as the sample of women with breast cancer (Table 4). Independent variables were forced into the equation in blocks based on our theoretical model. Sociodemographic factors were included in the first step (column 1); variables associated with risk of psychosocial morbidity were included as step number 2 (column 2), and in the third step, measures of the woman's resources, her personal strength (self-esteem), and social supports from family and friends were added (column 3). The tables include standardized regression coefficients (betas) that put each variable into the same scale for comparison. In this way, relative importance between variables can be determined.

Who Should Receive Intervention? And When Should They Receive It?

As expected, our results indicate that there are time effects (Table 3). Women who participated in the study during the first 3 months following surgery were more depressed; those participating 6-9 months following surgery were marginally more depressed than women participating at more distant times from surgery (12-15 months following surgery). The total equation is statistically significant but explains only 2% of the variance. These data suggest that early intervention may be important, as women are at risk for significant depression and mood distress in the first months after breast surgery. Since the time effects did not explain much variance, their importance should be interpreted with caution. Since it is theoretically plausible that there are interactions between having adjuvant therapy and time after surgery and age at diagnosis and time after surgery, these inter-

Table 1. Description of sample*

Patient characteristic	Healthy		Breast cancer	
	30-49 y†	50-69 y‡	30-49 y§	50-70 y
	% (No.)	% (No.)	% (No.)	% (No.)
Marital status				
Married	73.0 (114)	68.3 (125)	72.9 (167)	62.7 (271)
Widowed	1.3 (2)	10.4 (19)	2.2 (5)	19.0 (82)
Divorced	13.5 (21)	8.2 (15)	17.5 (40)	11.3 (49)
Single	12.2 (19)	13.1 (24)	7.4 (17)	6.9 (30)
No. of children < 21 y				
None	29.7 (46)	83.5 (152)	33.2 (76)	86.1 (371)
1	15.5 (24)	12.1 (22)	19.2 (44)	12.3 (53)
2	34.8 (54)	2.7 (5)	30.6 (70)	1.6 (7)
≥3	20.0 (31)	1.6 (3)	17.0 (39)	— (0)
Employed	67.9 (106)	38.0 (87)	65.5 (150)	45.1 (195)
Education				
High school	23.0 (35)	34.3 (60)	46.6 (105)	57.1 (241)
Some college	54.6 (83)	52.6 (92)	38.7 (87)	33.9 (143)
Graduate school	22.4 (34)	13.1 (23)	14.7 (33)	9.0 (38)
Socioeconomic status (mean and SD)	50.6 (10.2)	47.1 (10.7)	44.7 (12.2)	41.5 (11.9)
Ethnicity				
White	87.8 (137)	94.5 (173)	82.5 (188)	84.7 (365)
Other	12.2 (19)	5.5 (10)	17.5 (40)	15.3 (66)
Treatment				
Mastectomy	—	—	59.8 (137)	73.1 (316)
Mastectomy and RT	—	—	7.0 (16)	8.8 (38)
Mastectomy and CX	—	—	25.8 (59)	14.8 (64)
Mastectomy and CX + RT	—	—	7.4 (17)	3.2 (14)

*Unless otherwise specified, values in parentheses = number of patients. RT = radiation therapy; CX = chemotherapy.

†156 patients.

‡183 patients.

§229 patients.

||432 patients.

Table 2. Summary of measures

Variable	Measure	No. of items	Mean	SD
Social support	Perceived social support scale (Flamer, 1977)	15	11.13	13.34
Children < 21 y living at home	Household composition	1	0.70	1.13
Employment status	Currently employed	1	1.45	0.50
Age	Age at last birthday	1	(see Table 1)	
Socioeconomic status	Four factor index of social status (Hollingshead, 1965)	4	44.66	11.89
Marital status	Married, or living as married	1	0.69	0.46
	Widowed	1	0.10	0.30
	Divorced or separated	1	0.13	0.33
	Never married	1	0.08	0.28
Health status	National Health Survey, 1975	5	41.55	14.32
Burdens of treatment	Checklist of problems possibly due to breast surgery	14	17.61	3.18
Family support	Sickness Impact Profile (Gilson et al., 1975)	10	7.12	12.10
Social health	The Quantification of Social Contacts and Resources (Donald and Ware, 1982)	12	1.42	4.81
Life change	Recent life changes (Holmes and Rahe, 1970)	44	14.06	12.19
Self-esteem	Self-esteem Scale (Rosenberg, 1965)	10	23.15	14.58
Depression	Brief Symptom Inventory (BSI) (Derogatis, 1982)	6	8.20	12.3
Global Symptom Index	Brief Symptom Inventory (BSI) (Derogatis, 1982)	53	0.32	0.34

Table 3. Effect of time on depression following treatment for breast cancer (n = 661)*

Measure	B†	SE	Beta‡	P
0-3 mo following surgery	3.7	1.6	.12	.02
3-6 mo following surgery	1.9	1.6	.06	.25
6-9 mo following surgery	3.1	1.6	.10	.06
9-12 mo following surgery	-0.5	1.6	-.02	.74

*Adjusted R² = .02.

†Regression coefficient.

‡Standardized regression coefficient.

Table 4 Effect of sociodemographic factors, health factors, and social support on depression for healthy women and women with breast cancer (n = 1000)

Measure	Beta	P	Beta	P	Beta	P
Adjuvant therapy	.10	.01	-.10	.004	-.07	.03
No adjuvant therapy	.04	.35	-.08	.02	-.06	.08
Married	.001	.98	.01	.87	.02	.72
Widowed	.11	.02	.09	.02	.09	.01
Divorced	.15	.001	.10	.01	.08	.04
Age 40-49 y	-.08	.10	-.03	.50	-.04	.29
Age 50-59 y	-.12	.03	-.04	.38	-.06	.19
Age 60-69 y	-.15	.01	-.07	.20	-.09	.05
More children < 21	-.08	.06	-.05	.15	-.06	.06
Employed	.09	.01	.05	.14	.03	.27
Socioeconomic status	-.04	.20	-.01	.70	.03	.22
Burdens of treatment			.16	.0000	.14	.0001
Health status			.31	.0000	.23	.0000
Life change			.20	.0000	.14	.0000
Social health					-.04	.12
Poor self-esteem					.25	.0000
Social support					.09	.001
Family support					.19	.001
Adjusted R ²	.04		.27		.42	

actions were added to the model and tested using an omnibus F test. None of the interactions were significant, nor did they increase the variance explained by the model. Time effects were not found when the Global Severity Index was the dependent variable.

Who Is at Greatest Risk for Psychological Distress?

In the second analysis, we include a number of risk factors in addition to the two measures of cancer (surgical treatment alone or with adjuvant therapy compared with women who did not have surgery) and time after surgery. The potential risk factors based on the woman's sociodemographic background include age (40-49, 50-59, and 60-69 compared with 30-39), marital status (married, widowed, divorced compared to being single), socioeconomic status, employment status, and the number of children under 21 (zero to total number). These variables were forced into the equation as the first block (Table 4, column 1). Two dummy variables measuring breast cancer are included: "breast cancer and adjuvant therapy" and "breast cancer with no adjuvant therapy." With one exception, the intercorrelations between the independent variables were not sufficiently high to be concerned about multicollinearity. The correlation between

"health status" and "burdens of treatment" was $r = .62$. We explored the model with and without "burdens of treatment" and found only modest changes in the predictors, none that were statistically significant. Therefore, we concluded that the patterns did not reflect any important multicollinearity problems.

The results of the first step where only sociodemographic factors were included indicate that compared with younger women (30-39), women who are over 50 had greater depression and global symptoms. Women who are divorced have greater mood distress and depression than women who are single. Women who received adjuvant therapy were more depressed and had more global symptoms than did the nonsurgical group. Being a widow and the more children one has under 21 are also related to greater depression and overall symptoms. Neither one's socioeconomic status nor employment status increased one's vulnerability to psychological distress (Table 4, column 1).

In the second block, measures of health status were added (Table 4, column 2). Experiencing the side effects of treatment, poorer physical functioning, and poorer overall health status are independently related to greater distress and depression. All of the measures added were statistically significant and contributed to the variance explained (28% of the variance was explained). Both breast cancer groups were significantly different than the nonsurgical group; no age effects are found.

Consistent with the literature, these data suggest that the factors that increase one's risk for psychosocial morbidity are age (being younger), being divorced, being widowed, having more children under 21, experiencing side effects of treatment, poorer physical functioning, and overall perceptions of health.

In the third block, measures of one's personal resources, emotional strength (one's self-esteem), and social support (perceived emotional support, interaction with family, and involvement with family, friends, and social groups) are added to the equation. When these variables are added to the equation, the effects of having breast cancer without adjuvant therapy is no longer significant ($P = .08$) (Table 4, column 3). That is, the variation accounted for by breast cancer without adjuvant therapy appears to be mediated by one's self-esteem and support system. Women over 60 do significantly better than those under 40. The total equation is statistically significant and explains 43% of the variance.

When the Global Severity Index is the outcome measure, the pattern of findings is similar and the model is more explanatory (explaining over 50% of the variance.)

Psychosocial Interventions

While interventions for women with breast cancer are widely available, especially in metropolitan areas, few reports describing these interventions are found in the literature and even fewer studies assess their effectiveness in either reducing psychological morbidity or improving quality of life. These intervention strategies can be organized into three general categories—patient education (focusing on information control or case management); coping skills approaches with training in behavioral and cognitive management of the disruptive effects of cancer; and support groups that can focus on diagnosis and treatment issues, rehabilitation, and/or continuing care (22,23).

This review is limited to studies of women with breast cancer; as a result, it eliminates interesting related work on interventions for people with cancer. Readers desirous of this more complete treatment of the field are referred to two thoughtful and comprehensive reviews of this literature on psychological outcomes of interventions for people with cancer that have recently appeared in the literature conducted by Trisburg et al. (24) and by Andersen (25).

Patient Education

The best known approach to providing patient information and education is *Reach to Recovery*, a self-help program sponsored by the American Cancer Society since 1969. It was designed by and for women recovering from treatment for breast cancer and uses recovered "patients" as role models. While *Reach to Recovery* claims that its program benefits mastectomy patients (26), little evaluation of the program has been reported. One exception is a New York study of women who received a *Reach to Recovery* visitor (27). The intervention is brief, usually lasting for 30 minutes to 1 hour. From telephone interviews of 652 women, the investigators found that, regardless of age, level of education, or employment status, most women perceived the visit to be helpful. However, there were no significant differences in the emotional state of the women or on their return to former activities and routines.

Three studies report that counseling before or immediately after breast surgery is beneficial. In the first, Owens et al. (28) conducted a descriptive evaluation of "Informal Decision Analysis" for patients who were offered a choice of type of surgery and concluded that guidance in decision-making seemed psychologically beneficial to the women. Maguire et al. (29) found higher levels of problem recognition and referral among patients who received nurse counseling before and after breast surgery. Differences in psychiatric morbidity between those randomly assigned to counseling and controls (12% versus 39%) were not evident until 12-18 months after mastectomy. Bloom et al. (30) provided a *Reach to Recovery* volunteer and a nurse counselor to women immediately following breast surgery. The intervention provided information and support to women about rehabilitation following the surgery, about adjuvant chemotherapy, and about relationships to spouse, children, and friends. Initially, women offered the intervention reported more mood distress than a comparison group. Two months later, however, women participating in the intervention program were more likely to report a greater sense of efficacy. Mood distress differences as measured by the Profile of Mood States between the groups had disappeared.

Brief intervention can also be effectively delivered by telephone. Polinsky et al. (31) describe a case management program for 69 breast cancer patients that was delivered efficiently and aided reported improvements in physical, emotional, and social adjustment after surgery. Feasibility studies on the use of telephone counseling have recently been reported (32). In the first feasibility study, 115 breast and prostate cancer patients were asked whether they would use a telephone counseling service (in call) and whether they would be willing to have a pre-set counseling by phone (out call). Respondents indicated their

willingness to use the telephone counseling, slightly preferring the in-call strategy. In the second feasibility study, 30 women treated by the Eastern Cooperative Oncology Group for premenstrual breast cancer were interviewed. All but two (6%) of the women were willing to participate; none cut off the interview, and all answered questions regarding their psychosexual health, including questions regarding painful intercourse (33.3%), vaginal dryness (60%), fatigue (60%), and weight gain (80%) (32).

Educational interventions also can facilitate rehabilitation. Vachon et al. (33) compared women undergoing radiation therapy in a residential treatment facility to women living at home during treatment. The intervention included education, support, and behavioral strategies for improving coping; it lasted an average of 3 weeks. Significant decrements in emotional distress were reported by the intervention group. Interpretation of the findings is complicated by the difference in the living situation of the two groups. An exercise program for 114 women with breast cancer resulted in significant reduction in functional limitations, greater flexibility, and improved self-esteem, coping, and perceived support (34).

Counseling has also been advocated for sexual and reproductive issues of cancer patients. The limited studies indicate that when problems are not treated early, they can become irreversible. Regardless of format, counseling improves sexual functioning for breast cancer patients (2).

Educational interventions because they can be offered soon after diagnosis of breast cancer have an important role in the psychosocial aspects of care. Our data support the importance of the timing of these interventions to reduce depression associated with the diagnosis as a measure of preventive mental health.

Coping Skills Management

In a series of studies, Leventhal et al. (35) report on the adaptation to chemotherapy among a sample of 238 subjects, 167 of them with breast cancer. All of the women in their sample reported one or more unpleasant side effects that not only were the source of distress, but also interrupted daily activity. Different treatment regimens produced different side effects. However, the percentage of women reporting side effects was similar even though the treatment regimens differed.

Side effects appear to result from drug, personal, and environmental interactions and contain an important psychological component. The emotional response to the side effects is also generally equivalent across treatment regimens. Difficulties resulting from treatment and the worry due to cancer increase over the course of treatment. The meaning attached to these concerns varied as a function of disease stage (adjuvant treatment and recurrence). The failure to control side effects of treatment is related to subsequent distress, regardless of the reason for the treatment. The distress is related to the meaning attached to the side effects and appraisal of efforts to cope with them. They also found that patients focus on the stressor, i.e., the concrete and immediate concerns such as energy levels, the side effects of treatment, etc. One can conclude that intervention to reduce the stressor will reduce psychosocial morbidity and improve quality of life.

In addition to the side effect itself, the patient may experience nausea and vomiting in anticipation of the treatment. Behavioral methods have been successful in coping with anticipatory nausea and vomiting triggered by the treatment. The most common techniques used are relaxation training to block sensations of nausea, systematic desensitization which begins with the practice of relaxation and visualization of increasingly aversive stimuli, and cognitive or attentional distraction that involves blocking the perception of the nausea by involvement in a challenging task. All three approaches have resulted in reductions in duration, intensity, and frequency of anticipatory nausea (36-39).

The use of behavioral techniques are effective in alleviating distress in adults as well as in children. This distress is associated with greater depression and symptom severity as indicated by the analysis of the PABC. The samples of many of the studies reported include women with breast cancer, even though few studies are specific to breast cancer or to younger women (36,39). In one small albeit specific study, 19 women were randomly assigned to receive biofeedback training, cognitive therapy, or no treatment (40). Greater improvement in reported anxiety and urinary cortisol measures was found in the treatment groups. Because of the small sample size and high drop-out rate (26%), these findings should be viewed with caution. The use of self-hypnosis for pain relief has also been reported (41). The self-hypnosis training was provided as part of a support group for women with metastatic breast cancer; the intervention was evaluated separately (previously mentioned). Findings indicate that, in addition to reductions in pain intensity and duration among women susceptible to self-hypnosis, reductions in anxiety were reported. Patient education and support group interventions may also include behavioral techniques such as found in the study reported by Vachon et al. (33) and Spiegel and Bloom (41).

Support Groups

Support groups for cancer patients have generally been organized in one of three formats: self-help groups initiated by patients, counseling/therapy groups, and group psychotherapeutic models. In 1975 and again in 1985, the American Cancer Society conducted surveys of cancer support groups in California and found a tremendous growth in the number of groups, a trend toward education/discussion groups and away from counseling/therapy groups, a shift in the location of groups from community settings to hospital settings, and a broadening of the base for leadership in the group (42). A recent survey of the NCI Clinical and Comprehensive Centers (81% response rate) is consistent with these early findings of growth in support groups. All reporting Centers indicated the existence of active support groups (an average of 3.5 groups per Center). About one third of the groups were limited to one disease site, breast cancer. Most groups were composed of both patients and family members, although specific groups for family members or only for patients were also prevalent. Most groups were open-ended in format and met weekly to monthly. Support and education were the primary focus of groups, rather than cognitive-behavioral or

psychotherapeutic. Social workers and nurses led the majority of the groups (43).

Today, few groups have been organized specifically for younger women or for women of color. There are a few exceptions which are often with the encouragement of cancer patients. For example, locally, three young (under 40) women with metastatic breast cancer were instrumental in involving a psychiatrist and a nurse in the formation of a support group for African-American women (44). Support groups for Hispanic women have been formed in both Northern and Southern California. *Vital Options*, a Los Angeles-based organization and the only one representing young adults, has on-going support groups for both young (30-40 year olds) and younger (17-30 years olds) women with cancer (45).

The importance of social support for women with breast cancer is underscored in our analysis of the PABC: 15% of the variance in depression among our sample of women was explained by social support from family and friends. Yet, we don't know very much about whether support groups can substitute for support provided by family and friends. In our early work (46), we discovered that women who dropped out of the groups for reasons other than their physical health reported more religiosity. In Falke and Taylor's study, women joining support groups indicated that it was not a substitute for lack of support at home, but that they were unable to get as much support as they needed (47).

There are a few studies designed to evaluate the effectiveness of support groups in the literature (46,48-53). Three studies focus on women with cancer, two focus on metastatic breast cancer (46,54) and one on gynecological cancer (48). Cain et al. (48) studied the effect of individual, group, or no counseling for newly diagnosed gynecological cancer patients, using random assignment. The intervention included cancer education, diet and exercise management, learning relaxation techniques, expression of feeling, and goal setting. Women in the intervention groups reported significantly less anxiety and depression than the control groups 6 months following the intervention; no differences were found between delivering the intervention in a group versus individual format (48). Spiegel and Bloom (41), Spiegel et al. (46), and Spiegel et al. (54) published three reports of a randomized trial of group support and self-hypnosis training for women with metastatic breast cancer. Early findings indicated that the experimental group showed short-term advantages of better coping and less mood disturbance; decreased pain and suffering; and less anxiety, depression, and fatigue. Long-term follow-up when only three of the 86 women were still alive showed significantly longer survival for intervention patients of 36.6 months versus 18.9 months in the control group. Morganstern et al. (52) also reported findings suggesting a beneficial effect of a support program on survival. However, reanalysis of the data accounting for selection bias in matched controls revealed only a small, nonsignificant program effect. Fawzy et al. (55) have recently published data on the 6-year follow-up of their cohort of early-stage melanoma patients who were in a 6-week support group. To date, significantly fewer of the intervention group have recurrences (55). The better outcomes of the intervention group members may be due to better adherence to post-treatment recommendations (no smoking, protection from

sun) than the control group members (55). There are several studies currently under way to attempt replication of these findings. Currently, Spiegel and Spira (56), taking advantage of knowledge of immunology and new technology, are attempting not only a replication of the group support intervention, but also a better explanation of how group support gets translated into increased time of survival. Others attempting replication of these findings include the following: Schneiderman in Miami (57); Greer and Watson at Royal Marsden Hospital in London (58); Cunningham in Toronto (59); and Thoresen (60), another study at Stanford following an "at risk" cohort. In the spirit of this conference, it is hoped that all of these investigators will consider age as a potentially important intervening variable.

How does group support affect change in group members? The social interchange in the group can allow members to focus and to clarify a wide array of problems involving the course and treatment of their illness and their relationships with family, friends, and physicians. Each issue can be anxiety-provoking, but the groups can assist the individual to focus on the anxiety and thereby alleviate the individual's sense of helplessness in the face of problems. Second, groups can reduce the sense of isolation that individuals, especially those dying from cancer, experience. The group can also replace social support lost by withdrawal of family and friends. In some cases, learning how to talk to family and friends about their cancer reverses the process of mutual withdrawal that occurs. Third, groups can "detoxify" the process of dying, and by doing so, members can gain a sense of mastery over their situation. Finally, the importance given to the illness or death of a group member counteracts the withdrawal by her family and friends and reintegrates the individual into society (46).

In summary, interventions can be offered at time of diagnosis, before and during treatment, as part of rehabilitation following treatment, or as part of continuing care if the cancer has metastasized. While patient education interventions are mainly offered at time of diagnosis, they are sometimes offered during rehabilitation. Data from the PABC suggest that early intervention (e.g., during the first 3 months following diagnosis) may be important, as depression is greatest during this time. Since the burdens of treatment are strongly associated with psychosocial distress, coping skill interventions are critical throughout the course of active treatment. The literature review suggests that they can be offered at any time following diagnosis. Support group interventions are the most versatile and are offered at any time during the breast cancer trajectory (Table 5). The data analysis indicates that social support may explain as much as 15% of the variance and reduces the impact of breast cancer for younger women.

Table 5. Time and type of intervention

	Patient education	Coping skills	Support groups
Diagnosis	X		X
Treatment		X	X
Rehabilitation	X	X	X
Continuing care		X	X

Implications for the Future

A number of implications can be drawn from the review of the literature. First, the lack of research evaluating the effectiveness of interventions is inescapable. Few new studies have been published since a previous review of the literature on cancer in women in 1986 (61). We believe that this is due to the inherent difficulties in doing this type of research, especially the cost, and the lack of interest on the part of funding agencies to support it. Hopefully, this conference is a sign of renewed interest in this important research area. Second, the time is right for supporting such studies. While there is a lack of studies of intervention, there are many more studies of the factors putting a woman at risk for psychological morbidity. This was not the case in the 1970s, when the NCI initiated studies of intervention. We now have a better basis for determining when and who needs intervention. We also know a lot more about what interventions might be effective. Third, as we begin designing and testing interventions, cost must be considered. That is exactly why the studies of determining who is at risk are so important. If we know who is "at risk," then interventions can be targeted in a cost-effective manner. Low-cost interventions, such as cancer education, may be sufficient for most women, leaving greater resources for the 25% who have greater need. Fourth, efforts need to be directed to educating the oncology community on what has been called the "Third Phase of Medicine"—increasing the quality of life of women with breast cancer (62).

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Proceedings of a Workshop
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FOREWORD

The Workshop on Hereditary Breast, Ovarian, and Colon Cancer, sponsored by the National Cancer Institute and the National Center for Human Genome Research, was held on April 27-29, 1994, in Washington, D.C., to address the common issues related to hereditary cancers at these sites. Since this time, BRCA1 has been sequenced, BRCA2 has been localized, and two genes related to hereditary colon cancer have been identified. The rapid pace of research in this area continues.

While the study of genetic susceptibility offers unique opportunities to define the molecular mechanisms related to the development of cancer, it also offers unique challenges. These challenges include developing effective strategies for early detection, prevention, and treatment of hereditary cancers and defining effective approaches for counseling individuals from high-risk families concerning genetic testing. The potential benefits of testing for genetic susceptibility need to be balanced against the potential harm due to loss of privacy, loss of insurability, and, potentially, job discrimination.

We thank the speakers and session chairs for their participation in this effort. We believe that their thoughtful views have helped articulate issues that need future consideration. We also gratefully acknowledge the expert reviewers of the manuscripts published in this monograph. Without their substantial contribution, this monograph would not have been possible.

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Translational Research on Hereditary Colon, Breast, and Ovarian Cancers

Frederick P. Li*

Discoveries of inherited cancer susceptibility genes are creating new opportunities for translational cancer control research. Identification of these genes was facilitated by epidemiologic studies of mendelian patterns of cancers in families and advances in laboratory techniques to detect inherited mutations. Tumor suppressor genes were the first cancer-predisposing genes identified, primarily through studies of rare cancers such as hereditary retinoblastoma and Wilms' tumor. Recently, a second class of susceptibility genes, mismatch repair genes such as MSH2 and MLH1, has been shown to be defective in hereditary nonpolyposis colon cancers. Knowledge of these genes and the recently identified BRCA1 gene for hereditary breast/ovarian cancers raises the possibility of cancer-predisposition testing of substantial portions of the general population. Carriers are at high risk of cancer and are candidates for early detection and chemoprevention studies. However, large-scale cancer-predisposition testing poses questions about not only ethical, legal, and social issues, but also technological and logistical challenges. Cancer-predisposition testing is new, and research is needed to maximize benefits while minimizing risks. [Monogr Natl Cancer Inst 17:1-4, 1995]

Recent advances in molecular and genetic epidemiology have expanded vistas for research on cancer prevention and early detection. This overview examines the accomplishments to date and identifies some challenges to the conduct of translational research on hereditary cancers. For purposes of this presentation, translational research signifies the applications of basic discoveries in the molecular biology of inherited cancer predisposition to reduction of disease morbidity and mortality.

Epidemiologic studies show that virtually all forms of cancer have a tendency to aggregate in families (1). Close relatives of a cancer patient can be considered to have increased risk for that form of cancer and perhaps for other cancers. The fraction of a cancer that is hereditary (number of hereditary cases/total number of the cancers) varies substantially. Inherited susceptibility accounts for a high proportion of certain rare forms of cancer, such as retinoblastoma of the eye (2), but for a much smaller proportion of lung cancers that result primarily from cigarette smoking.

Members of certain cancer families are at exceptionally high risk and can be studied as human models of cancer susceptibility (3). To identify inherited susceptibility genes, clinical observations have helped to identify affected families for epidemiologic studies to quantitate their excess risk. Complementary

laboratory studies can clarify the biological basis of susceptibility, including mapping and cloning of inherited cancer-predisposing genes. The studies have revealed important classes of cancer-associated genes, such as tumor suppressor genes and, more recently, mismatch repair genes. In these studies, affected families and tissue specimens provided by clinicians and epidemiologists have been essential to the molecular discoveries by laboratory scientists. Basic discoveries, in turn, create new clinical applications to reduce cancer morbidity and mortality.

Retinoblastoma is a prototypic hereditary cancer in humans. Mutations in the retinoblastoma gene, even single-nucleotide alterations, confer a 90% likelihood of cancer development (4). Carriers often develop multiple lesions in both eyes at unusually early ages and subsequently develop second primary cancers of other organs. On the basis of studies of retinoblastoma, Knudson (5) developed his two-mutation model, which provided the conceptual framework for studying rare family aggregates of cancer to gain new understanding of human carcinogenesis. Knudson proposed that at least two mutations are required to transform a normal cell into a cancer cell. At the molecular level, familial and sporadic (nonfamilial) forms of a cancer involve the same gene(s). In sporadic cancers, no mutation is inherited and at least two somatic mutations must occur within one cell. Hereditary cancer is due to a germinal mutation that has been inherited from a parent and propagated in all somatic cells of susceptible family members; a second and subsequent set of mutations transforms the cell. The hypothesis implies that somatic cells of cancer gene carriers can be examined for the first mutation. A comparison of the tumor cells and somatic cells of these patients can reveal the second and subsequent mutations. Thus, the complex process of human carcinogenesis can be separated into two components in hereditary cancers for ease of study; the results are applicable to the sporadic (nonhereditary) form of that cancer.

Most known tumor suppressor genes have been discovered through studies of families with hereditary cancers (3). In addition to the RB1 gene for hereditary retinoblastoma on chromosome 13q14, studies identified the WT1 gene for Wilms' tumor on chromosome 11p13 and germline p53 mutations in families with diverse childhood cancers and early-onset breast cancer (Li-Fraumeni syndrome). Subsequent studies identified

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the NF1 and NF2 genes for neurofibromatosis (types 1 and 2, respectively), the VHL gene for renal cancer associated with von Hippel-Lindau disease, and the APC gene for adenomatous polyposis coli. Recently, germline mutations in the RET oncogene were identified in multiple endocrine neoplasia (type 2) and in related cancers. Mapping and cloning of these genes have been facilitated by the finding of large, affected families or constitutional chromosome markers and the rarity of phenocopies.

Identification of genes that cause hereditary breast, ovarian, colon, and other common cancers has been more challenging. Familial cancers can be due to shared environmental influences or chance association, which can be difficult to distinguish from hereditary cancers. In addition, family histories of cancer might be erroneous; the error rate for the primary site of cancer is 20% for close relatives and 40% for distant relatives (6). In the United States, one person in three develops an internal malignant neoplasm during his or her lifetime. The 250 million Americans nationwide form many striking family aggregates of cancer by chance. A family history of the common forms of cancer is, therefore, the rule and not the exception. Only a fraction of families with a history of cancer transmits a heritable susceptibility gene. Several clinical features have been described that can help identify hereditary cancers: (a) specificity of the cancer site or tissue of origin among affected relatives, (b) earlier age of occurrence than is usual for that neoplasm, and (c) multifocal cancers of different colon origins within one or several susceptible organs.

Hereditary nonpolyposis colon cancer (HNPCC) is the common form of dominantly inherited colorectal cancer. HNPCC has been operationally defined as the presence of colorectal cancer in at least three blood relatives, including two first-degree relatives, in two consecutive generations; at least one of the colorectal cancers was diagnosed in the individual before 50 years of age (7). HNPCC has been estimated to account for approximately 4% of all colorectal cancers in the United States (7,8). HNPCC has been further divided into two categories: 1) hereditary site-specific nonpolyposis colonic cancer (Lynch syndrome I) and 2) cancer family syndrome (Lynch syndrome II). Patients with Lynch syndrome II develop not only colorectal cancer, but also cancers of the endometrium, ovaries, and other sites (9). Lynch syndrome II is difficult to study because colorectal cancer and its 10 or more associated cancers (endometrial, ovarian, bladder, breast, kidney, larynx, pancreas, stomach, small bowel, and ureter) make up one half of all cancers in the U.S. population. Millions of U.S. families have cancer histories that mimic Lynch syndrome II but that are phenocopies.

Advances in knowledge of the molecular genetics of colorectal cancers have been facilitated by the availability of tissues through several stages of progression of normal colonic cells to small adenomas, large adenomas, and carcinomas (10). The average colon carcinoma has lost nearly 20% of all alleles within its genome in a nonrandom distribution (11). This loss of alleles includes chromosome 5q deletions that span the APC gene for adenomatous polyposis coli and a second colon cancer-associated gene, MCC (mutated in colon cancer). Deletions of chromosome 17 involve the p53 tumor suppressor gene (also known as TP53), and deletions of chromosome 18 involve the DCC (deleted in colorectal cancer) gene (12). In addition, al-

terations in DNA methylation and activating mutations of ras and myc oncogenes have been found in colon cancers.

The inherited defects in HNPCC were unknown until a series of breakthroughs were reported starting in May 1993. Peltomäki et al. (7) reported genetic mapping of a human HNPCC locus to chromosome 2p. In colon cancer specimens of familial and sporadic cases, these and other investigators described the finding of microsatellite instability at multiple loci (13). The findings suggested that the HNPCC locus on chromosome 2p might be a mismatch repair gene, which normally repairs replication errors in microsatellites. This hypothesis led the geneticists Fishel, Kolodner, and co-workers (14) to examine the human homologue of several yeast mismatch repair genes as candidate HNPCC genes. Their functional cloning studies and the parallel positional cloning studies by Vogelstein, de la Chappelle, and colleagues (15) identified the human MSH2 gene for HNPCC. Another mismatch repair gene, MLH1, was soon identified as a second HNPCC gene (16). Additional mismatch repair genes in lower species are being studied as candidate genes for human cancer development.

New opportunities for translational research and interventions have resulted from identification of the MSH2 and MLH1 genes for HNPCC and from the mapping and recent cloning of BRCA1 and other breast/ovarian cancer genes. Interventions to reduce colon cancer morbidity and mortality might include intensive screening for detection of precancerous colonic polyps, dietary modification and chemoprevention with aspirin, non-steroidal anti-inflammatory agents (sulindac), and vitamins and/or micronutrients (17-19). For BRCA1 carriers, interventions under consideration include prophylactic oophorectomy/mastectomy and use of tamoxifen or other hormones as chemopreventive agents (20). However, genetic predisposition (predictive) testing to identify carriers of cancer susceptibility genes is new. Legal, ethical, and social issues of testing are of growing concern to the National Center for Human Genome Research, various professional and governmental organizations, and the general public (21). A study of the population in Utah has shown that 83% of respondents had an interest in undergoing colon cancer-predisposition testing (22). Similar enthusiasm for cancer-predisposition testing was found among relatives of breast cancer patients (23). The actual proportion who will present for such testing is likely to be much lower, based on the Huntington disease experience.

To date, only a few small pilot cancer-predisposition testing programs have been developed for inherited mutations in the p53, APC, RET, and RB1 genes (24). Participation in these studies has been limited primarily to high-risk relatives of cancer patients in whom a germline mutation has been identified. The lesson from these programs might be applicable to HNPCC and other common cancer-predisposing genes. The goal of research programs in predisposition testing should be to maximize the benefit and minimize psychological, social, and economic risks to participants. General agreement exists regarding adherence to the four ethical principles of respect for autonomy, beneficence, confidentiality, and justice (21). However, interpretations of these principles in specific clinical situations can differ among scholars of diverse disciplines as well as among the general public. The National Advisory Council for Human

Genome Research has recently published a statement advising pilot research studies of predisposition testing to evaluate the potential for both benefit and harm (25). On the other hand, some biotechnology companies perceive a public demand and propose to offer testing as a service to healthy members of the general population. Conflicting approaches are likely to confuse the public, but developing consensus among providers is a challenge in a free-enterprise society.

More attention is needed to the validity of laboratory assays in cancer-predisposition testing. Standard measures of test validity are sensitivity, specificity, and predictive value (positive or negative) (26). Sensitivity is the fraction of carriers of a cancer susceptibility gene who are found to have a mutation on testing. Specificity is the fraction of noncarriers whose test result is normal. Predictive value positive is the proportion of true carriers among those reported to have a mutation on testing. Predictive value negative is the proportion of noncarriers whose genetic test result shows no mutation. The issue of validity has surfaced as the pool of potential test subjects has been expanded for the common cancer genes to include substantial segments of the general populations. If one assumes a sensitivity of 90% and a specificity of 95% for a genetic test and a prevalence of colon cancer susceptibility genes of one in 200 in the general population, the predictive value of a positive test result in the general population is 8.3% (Table 1). In other words, only 8.3% of the general population who have an "abnormal result" are actually predisposed to colon cancer. However, for purposes of early diagnosis and other interventions, 100% of those with a positive test are likely to be offered costly and potentially harmful interventions, such as annual colonoscopies at approximately \$1000 per test (19). Higher than 90% sensitivity and 95% specificity might not be achievable if the mutant nucleotides have not been identified previously in an affected relative, and the potential sites of mutation are widely scattered throughout thousands of nucleotides within these colon cancer genes. Even if it were possible to increase both sensitivity and specificity to 98%, the predictive value positive is 20% when the carrier frequency among study subjects is one in 200. The same issues apply to predisposition testing for BRCA1 in the general population.

By focusing on high-risk subjects, the predictive value of the test can be substantially increased (26). Even maintaining 90% sensitivity and 95% specificity, the predictive value positive rises to 81.8% if the carrier frequency is one in five among high-risk subgroups, such as close relatives of colon or breast cancer patients who have a known mutation. However, the restriction

would preclude identification of certain carriers, such as subjects with no living affected relatives. In any testing program, subjects need to be counseled that testing does not predict with certainty whether cancer will develop or when the disease might appear.

Additional challenges exist with regard to the logistics of coordinating cancer-predisposition testing for MSH2/MLH1 and other prevalent cancer susceptibility genes among multiple centers in the United States. The New England region, for example, not only is densely populated, but also has a high concentration of health care institutions. There are five federally designated comprehensive cancer centers and a total of nine medical schools. These centers have affiliated teaching hospitals and community hospitals that provide care for nearly 10 000 colon cancer patients and 10 000 breast cancer patients diagnosed annually in New England residents. Several of these centers are in various stages of preparing or establishing genetic predisposition testing programs for colon cancer and breast cancer. A regional plan is needed for colon and breast cancer-predisposition testing research that will optimize the benefit-to-risk ratio for affected families and the community. The alternative approach of competing programs will increase the likelihood of confusion and harm. Competition might also hinder the collection of adequate numbers of carriers for intervention trials. These concerns have prompted efforts to convene a working group of staff from New England medical schools and teaching hospitals to discuss testing. The multidisciplinary group consists of physicians (particularly geneticists, surgeons, oncologists, and gastroenterologists), nurses, psychologists, genetics counselors, ethicists, and other parties. An initial goal is to develop a set of recommendations regarding the basic principles and practices that should be part of colon cancer genetic testing programs in the region. The recommendations would be disseminated to the health care community and assessed for short-term impact on knowledge and practice.

The goal of translational genetic predisposition research is the reduction of cancer morbidity and mortality. To assess the effectiveness of predisposition testing and interventions, randomized studies with long-term follow-up are needed on large groups of carriers. These multidisciplinary studies will need to involve additional specialists in pharmacology, chemoprevention, radiology, endoscopy, biomarker research, and other relevant areas.

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Table 1. Cancer-predisposition testing of 10 000 persons*

Results	No. of subjects with predisposing mutations		
	Present	Absent	Total
Test positive (mutant)	45	498	543
Test negative (normal)	5	9452	9457
Total	50	9950	10 000
Predictive value positive	45/543 = 8.3%		
Predictive value negative	9452/9457 = 99.9%		

*Prevalence of mutations was 1:200, test sensitivity was 90%, and test specificity was 95%.

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Hereditary Cancers: From Discovery to Intervention

Alfred G. Knudson, Jr.*

This conference concerned hereditary cancers of the breast, ovary, and colon, which are the common, often fatal, cancers with the greatest heritability in their causation. Four genes whose mutations impart dominantly heritable predisposition to one or more of these cancers have been cloned and one more has been mapped. The most molecular details are known for colon cancer. The APC gene of familial polyposis coli leads to the accumulation of numerous polyps, but the probability of transformation of the latter to cancer is low. This provides the opportunity to monitor putative preventive measures with an intermediate end point. In hereditary nonpolyposis colon cancer, transformation of the polyp to cancer is accelerated by an inherited mutation in either of two DNA mismatch repair genes. The discovery of an intermediate end point could be very helpful for breast cancer. Testing persons at risk for predisposing mutations depends heavily on the availability of promising measures for prevention or treatment. [Monogr Natl Cancer Inst 17:5-7, 1995]

If we accept the idea that mutations are the causative mechanism for cancer, then we become immediately interested in the targets of those mutations, cancer genes, and in their causes. We acknowledge that some mutations, both germinal and somatic, occur at a spontaneous or background rate, and that genetic and environmental factors can both increase the probability that cancer will occur. Four categories of persons, or oncodemes (1), can be imagined, according to the presence or absence of genetic and environmental variants (Table 1).

The first two categories seem to account for most cases, e.g., probably 95+% of retinoblastoma cases, with about 60% in the first category and 40% in the second. Such cancers should have a rather even incidence around the world. However, most cancers, perhaps 80%, involve environment in their origin, but many of them may also involve heredity. Thus, many lung cancers may occur among smokers of particular genotypes (e.g., active phase

I enzymes or inactive phase II enzymes for the metabolism of procarcinogens). Genes in the second oncodeme will generally be subject to strong negative selection and will thus be uncommon in a population, held there by recurrent germline mutations. Some fraction of germline cases will therefore have a negative family history, even if penetrance is high. Persons carrying such genes may have a very high relative risk for developing a tumor, but the population-attributable risk will usually be low. On the other hand, persons in the fourth oncodeme may have modest relative risks, but the attributable risk may be high. We have been concerned in this conference primarily with persons in the second oncodeme.

In particular, we are concerned with those who have a dominantly inherited predisposition to cancer of the colon, breast, or ovary. Among the commonly fatal cancers, these are the cancers with the greatest heritability in their causation. A consideration of pedigrees showing dominant inheritance reveals that penetrance is seldom complete; that is, some gene carriers do not develop cancer in an entire lifetime, indicating immediately that the mutant gene is not a sufficient condition. We also note that predisposition is never to all cancers; indeed it may even be to a single kind of cancer. Another feature is that the age-specific incidence curve for a particular cancer may be shifted to an earlier than usual age. The most readily recognized heritable cancers are those that 1) occur during, or even after, the age of reproduction, so that affected families of two or three generations may be found, 2) have a penetrance of 50% or more, and 3) have a reasonably high incidence (> one per 10 000 persons). Three conditions of interest here show these features: familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC), and hereditary breast (and ovarian) cancer associated with the BRCA1 gene. Progress in finding the genes responsible for dominantly inherited cancers has been rapid over the past few years, with the result that a dozen or so, including those for FAP and HNPCC, have been cloned, and that some others, including BRCA1, have been mapped.

The genes of interest here are four (APC, hMSH2, hMLH1, and TP53) that have been cloned and one (BRCA1) that we expect to be cloned soon (2-9). Most of the genes that have been cloned or mapped are apparently antioncogenes, or tumor suppressor genes, including APC, TP53, and probably BRCA1 (10). Multiple endocrine neoplasia type 2 (MEN2), and proba-

Table 1. Oncodemes*

Oncodeme	Heredity	Environment
Background	-	-
Genetic	+	-
Environmental	-	+
Interactive	+	+

*- = factor not operating; + = factor operating.

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See "Note" section following "References."

bly the Beckwith–Wiedemann syndrome, involve oncogenes, whereas HNPCC, or Lynch family cancer syndrome type 2, so far involves two DNA mismatch repair genes. Both oncogenes and antioncogenes operate at various points in signal transduction (cell membrane, cytoplasm, and nucleus), suggesting the existence of both positive and negative controls at multiple stages in transduction. Since the published pedigrees of hereditary cancer suggest as many as 50 or so different forms of hereditary cancer, and since most of the known cancers are attributable to antioncogene mutations, that category of cancer genes could grow to approach that of oncogenes in size.

I should like to emphasize that some persons with germline mutations in the genes of interest to us here do not have a positive family history, because they represent new mutations. The frequency of this phenomenon varies considerably from condition to condition. For example, about 80% of heritable cases of retinoblastoma are new germline mutants, and about 50% of NF1 cases are newly mutant. The percentage will probably prove to be about 25% for the Li–Fraumeni syndrome and for FAP and will almost certainly be lower for HNPCC and BRCA1. All of these conditions are maintained in a population by recurrent mutations. A mutational equilibrium is reached in which the numbers of persons affected by new mutations is balanced by the diminished numbers of offspring among those affected; mutation and selection achieve a balance. Preventive strategies must take this into account. Thus, if no persons with NF1 reproduced, the incidence of the disease would become 50% of its present value, not zero. If we were to rely only on family history, just 50% of NF1 cases would be recognized. Therefore, a person with the phenotype of FAP and a negative family history should be checked for APC mutation, in which case 50% of his/her offspring would be at risk. Similarly, any patient whose colon carcinoma shows the replication error phenotype should be checked for mutation in the hMSH2 and hMLH1 genes. Of course, some of these tumors should prove to be replication error-positive because of somatic mutations at one of these loci.

The hereditary cancers have already had importance beyond their numbers. They have pointed to most of the antioncogenes that have been discovered and to a role for mismatch repair in human cancer. The genes responsible for them may also suggest new approaches to cancer treatment, even replacement of defective genes. However, even now some persons at risk of cancer can be identified by genetic analysis, and at this conference we have been considering when this should be done, what subjects should be told, and what interventions should be undertaken. The answers to these questions are obviously a function of the ease of detection of a genetic condition, the age at which cancer develops, the presence of intermediate preneoplastic or benign neoplastic states, and the availability of satisfactory preventive or therapeutic measures. The offspring of a person who has had bilateral retinoblastoma should be checked immediately after birth, or even in utero, because early detection and cure can be accomplished. Persons at risk of colon, breast, or ovarian cancer do not require such early testing until preventive measures become available.

Colon cancer is particularly instructive, because it appears that polyps are precursors in most, if not all, cases. However,

FAP teaches us that the probability that a polyp will become malignant is very low, which makes it a good intermediate end point for evaluation of preventive measures and a target of therapy by excision in sporadic cases. Molecular examination of polyps suggests that the mutation or loss of both copies of the APC gene is necessary; i.e., the polyp is a “2-hit” lesion (11,12). Some of the polyps, especially large ones, also show mutations in KRAS. The net result is that there is an increase in the number of cells, especially stem cells, available for conversion to carcinoma by other events, such as mutation in TP53 and DCC. This theme of the importance of stem cell replication is repeated in many examples of carcinogenesis. Thus, chronic ulcerative colitis probably predisposes to colon cancer by a similar mechanism, increasing the probability that critical mutations will occur (13). Similarly, inherited mutation in the RET oncogene causes C-cell hyperplasia in the thyroid (14,15). Another example is the physiologic stem cell proliferation in the developing retina, kidney, and adrenal medulla, which provides the opportunity for clonal growth of once-hit cells that are precursors of retinoblastoma, nephroblastoma, and neuroblastoma and may account for the fewer events found in these tumors (16). A similar physiologic growth occurs in the breast at puberty, rendering this target tissue different from other epithelial tissues. This may explain why the Li–Fraumeni syndrome predisposes to breast cancer but not to other cancerous epithelial tumors, such as colon carcinoma, in which somatic mutations in TP53 occur at a high rate. In effect, more events are necessary for colon cancer than for breast cancer, at least at an early age, so the impact of inheriting one of the steps to cancer is greater for the latter. This same phenomenon is observed for inherited mutations in RB1. The penetrance for retinoblastoma is about 95%, but for osteosarcoma, which commonly also manifests TP53 mutations, is about 10%; no increased risk is discernible for small cell carcinoma of the lung, which usually shows not only mutations at RB1 and TP53, but also deletion in chromosome 3p.

The existence of two well known hereditary conditions, FAP and HNPCC, that predispose to colon cancer, raised a question about the existence of two pathways to its formation. The discovery of the genetic bases for nearly all cases of HNPCC has now settled that question. Mutations in hMSH2 and hMLH1 cause defects in repair of errors in DNA replication. A somatic mutation or loss of the second copy of these genes produces a recessively crippled cell, thereby greatly increasing the rates of mutation at genes important for carcinogenesis in the various target tissues in patients with HNPCC. For the colon, these mutations affect the APC, KRAS, and TP53 genes at the same rates observed in sporadic colon cancer. The pathway is apparently the same, but transit along the pathway occurs much more rapidly. This may account for the failure to observe many polyps in patients with HNPCC, because polyps are much more readily converted to carcinomas. For colon cancer, the path seems to be constant, regardless of predisposing cause. Intervention then can perhaps take advantage of the multiple steps required by attempting to reduce the rate of passage from one step along the way to the next. Prevention of polyps would therefore seem to make good sense. If a satisfactory method for doing so could be found, it should be implemented early in the life of the

susceptible person, because attempts should be made to reduce the probability of each event, including mutation or loss of the second copy of the APC gene. We note, for example, that the number of polyps in patients with FAP begins to increase sharply at the age of 10-12 years. Clearly, the age for testing and informing persons at risk will depend on the availability of means of intervention. However, we must consider the possibility that trials of promising agents might be more informative if they are begun at an early age.

In any case, the promise of preventive intervention is greater for tumors that entail multiple events. Colon cancer holds much more promise for prevention than does retinoblastoma. On the other hand, the rapid growth to malignancy when the number of events is small produces more homogeneous tumors, genetically speaking, so therapeutic response could be expected to be more uniform for cells of a tumor produced by a few events than for one produced by multiple events. If this conclusion were true, emphasis should be on the treatment of tumors in children and on the prevention of common cancers in adults. The existence of great risk for colon cancer in patients with HNPCC emphasizes the enormous effects of increasing the rate at which each event occurs. Suppose, for example, that such a condition increases the rate of mutation 100-fold. If just two events were necessary, there would be a multiplier effect of 10^4 . This would be more than negated by the need for mutation at the second copy of the HNPCC gene, hMSH2 or hMLH1. On the other hand, a sequence of four events would involve a multiplier of 10^8 , which would more than compensate for the need for an extra event. Similarly, any measure that could reduce mutation rate should have a much greater effect in reducing the probability of a multistep tumor than a two-step tumor. A corollary of this argument is that a measure that can reduce the probability of cancer in a person who has a genetic predisposition to cancer should be even more beneficial in a person who has no such predisposition.

For breast cancer we are eager to know about BRCA1, which should be cloned soon. Is it a step for all breast cancers or is breast cancer more heterogeneous than colon cancer with respect to pathogenetic pathway? Can we devise a means to recognize some precursor state, homologous to the polyp for colon cancer? The same questions pertain to ovarian cancer. Better information about genetic changes and about intermediate end points is necessary for both.

Critical for all of the cancers discussed here is a need for effective means of intervention, be it preventive or therapeutic.

Prevention appears at this time to be a more promising approach. Meanwhile, we consider carefully, as discussed at this meeting, what we tell families and when we tell them about risks for these cancers, remembering that our opinions should be subject to even drastic change when effective measures of intervention are forthcoming.

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Genetic Analysis of Eight Breast–Ovarian Cancer Families With Suspected BRCA1 Mutations

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BRCA1 is a breast cancer-related tumor suppressor gene located on human chromosome 17q21. Inherited mutations in **BRCA1** are thought to be responsible for approximately half of all inherited breast cancer and to confer increased risk for ovarian, colon, or prostate cancer. Studies of affected families and population-based studies have provided some information on the prevalence of **BRCA1** mutations in Caucasian U.S. and European populations as well as on the penetrance of these mutations. We review the available data on the epidemiology of breast cancer with specific reference to **BRCA1**. In addition, we describe the genetic analysis of one large family with multiple affected individuals now known to harbor a **BRCA1** germline mutation but initially identified by genetic linkage analysis. This family is presented as a model of the challenges that can be encountered in genetic analysis of familial forms of cancer. To this end, we compare the outcome of analysis before and after the identification of a mutation that predisposes family members to early-onset breast and ovarian cancers. We describe seven additional families with evidence of linkage between breast cancer and genetic markers in the **BRCA1** region. Each of these families generated a 2-point LOD (i.e., logarithm of the odds) score greater than 1.18 for at least one polymorphic marker flanking **BRCA1**. These families have formed the basis of our efforts to characterize **BRCA1** mutations. First-pass mutation analysis using the single-strand conformation polymorphism approach failed to identify any mutations in the seven families. We consider the possible reasons for the apparent low mutation-detection efficiency. [Monogr Natl Cancer Inst 17:9-14, 1995]

Family history has long been identified as a risk factor in the development of breast cancer. Until recently, however, attempts to identify the genetic basis of familial breast cancer have been unsuccessful. There were previous indications that familial breast cancer was a distinct clinical entity—age at onset for familial breast cancer is considerably younger than for sporadic cases, the prevalence of bilateral breast cancer is higher, and the presence of associated tumors in affected individuals is noted in

some families. However, inherited breast cancer does not appear to be distinguished by histologic type, morphologic grade, metastatic pattern, or survival characteristics. In addition, data collected as part of the Cancer and Steroid Hormone (CASH) Study suggested that there was a cohort of women with two or more first-degree relatives with breast cancer who were at extraordinarily high risk of developing breast cancer. The CASH Study dataset, comprised of almost 5000 women with breast cancer diagnosed before age 55 and an equal number of age-matched control subjects, provided relative risk estimates of developing breast cancer based on family history (1). These data suggest that, while having a mother or sister with breast cancer increases risk 2.5-fold and having a grandmother or aunt with breast cancer increases risk 1.5-fold, women with both a mother and a sister with breast cancer have a dramatically increased risk of developing breast cancer that is 14-fold higher than that for a woman with no family history of breast cancer. This study has been criticized as overestimating risk, and it now appears that the study cohort may have contained more women with inherited breast cancer than is usually found in population-based studies, possibly because of the selection of women diagnosed at an early age. Following the publication of the CASH Study

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See "Notes" section following "References."

data, several studies, at least one of which included a subset of the families included in the CASH Study analysis, suggested an autosomal dominant pattern of inheritance for breast cancer susceptibility in selected families (1-4).

A major breakthrough occurred in 1990 when, despite widespread skepticism that breast cancer would ever be attributed to a single gene, genetic linkage analysis of several families with apparent autosomal dominant inheritance of early-onset breast cancer identified seven families which defined a region on chromosome 17q thought to contain a susceptibility gene, now termed "BRCA1" (5). This result was subsequently confirmed and extended to include ovarian cancer (6). With these new data came the ability to study affected families individually. Investigators from Europe and the United States provided data on such families to the Breast Cancer Linkage Consortium, resulting in a collaborative study of 214 breast cancer families, including 57 breast-ovarian cancer families. Analysis with genetic markers from the BRCA1 candidate interval on chromosome 17q12-21 suggested that more than 90% of breast-ovarian cancer families showed linkage of disease to the markers (7), while about 45% of families with apparent autosomal dominant transmission of breast cancer, but without incident ovarian cancer, demonstrated linkage between breast cancer and the 17q12-21 markers. The consortium also estimated that women with evidence of a germline BRCA1 mutation had an 85% lifetime risk of developing breast cancer and an increased, but less well defined, risk of developing ovarian cancer. More recently, using a subset of the original families, the consortium found evidence for an associated fourfold increased risk of developing colon cancer and a threefold increased risk of developing prostate cancer in male mutation carriers (8).

In an effort to isolate BRCA1, studies of recombination events in BRCA1-linked pedigrees progressively reduced the size of the BRCA1 candidate region by localization of the proximal and distal boundaries at THRA1 and D17S579 (9), then at THRA1 and D17S183 (10), then at RARA and D17S78 (11), and most recently at D17S857 and D17S78 (12), a distance estimated to be approximately 1.0 Mbp. The BRCA1 region excluded several previous candidate genes, including ERBB2, thyroid hormone receptor α (THRA1), NME1, prohibitin (8,9), and retinoic acid receptor α (RARA) (10). Furthermore, no disease-associated germline mutations were found in the 17 β -estradiol dehydrogenase gene (EDH17B2) by sequencing in affected individuals (10), strongly suggesting that EDH17B2 was not BRCA1.

Skolnick and colleagues (13) recently announced the identification of this important gene. BRCA1 is a novel gene spanning a genomic region of more than 100 Kbp encoding a protein of 1863 amino acids. Three of the four mutations described in the initial reports are distinct point mutations in the 3' end of the gene, and the fourth appears to be a regulatory mutation that results in loss of the BRCA1 transcript. Subsequently, three reports (14-16) were published describing another 22 mutations. A total of 38 independent mutations have now been reported; 77% of these mutations are frameshift or nonsense mutations resulting in truncation of the protein product (17). While these reports suggest that future studies will be complicated by the large size of this gene and its protein product, this finding paves

the way for intensive study of the function of BRCA1 as well as the means of testing individuals at risk of harboring BRCA1 germline mutations and providing associated risk counseling.

As part of the effort to identify BRCA1, genetic analysis of numerous families with inherited susceptibility to breast and ovarian cancers was performed. In this study, we report the genetic analysis of a newly identified branch of an extended family previously reported as linked to BRCA1 (9). While studying this family, we encountered a variety of problems. 1) Several key individuals were found to have the affected haplotype but had not developed breast-ovarian cancer by age 53 years or prior to death, making clinical counseling difficult. 2) A recombination event was predicted in the reconstructed haplotype of one of the unaffected individuals. 3) The haplotype of the individual possessing the putative recombination event was uncertain because of the unusual fashion in which it was generated. The inferred haplotype and recombination event in this individual would have significantly narrowed the size of the BRCA1 candidate region under investigation prior to the identification of the BRCA1 gene.

We present the rationale behind the reconstruction of the uncertain haplotype and compare the predicted diagnostic outcome by linkage analysis with the known outcome following identification of the predisposing mutation in the BRCA1 gene of this family. Seven new families with multiple affected individuals were also analyzed for linkage and BRCA1 mutations and were found to have evidence of linkage to the BRCA1 region. These seven families were screened for BRCA1 mutations by single-strand conformation polymorphism, and no mutations were identified.

Materials and Methods

Family Collection

The ascertainment of family 15 has been described previously (9). Family 46 was also identified and followed at the University of Michigan Medical Center. Families 28, 30, 34, 77, 130, and 178 were identified at the Dana-Farber Cancer Institute. Blood samples (20 mL) were collected from each individual. Half the sample was used for genomic DNA preparation from peripheral blood lymphocytes and half for lymphoblastoid cell line generation by Epstein-Barr virus immortalization.

DNA Analysis

Nineteen polymorphic polymerase chain reaction (PCR)-based markers were typed on family 15 in this study, and five are reported on here. The markers (D17S1138, D17S1139, D17S1144, D17S1145, D17S1147, D17S1142, D17S250, THRA1, D17S846, D17S856, D17S1185, EDH17B-DEL, EDH17B-A3T, D17S858, D17S859, D17S183, D17S579, D17S409, and D17S588) are available through the Genome Data Base (GDB, The Johns Hopkins University, Baltimore, Md.). The markers have been placed in order from centromere to telomere as follows: D17S250, THRA1, D17S846, D17S856, D17S1138, D17S1139, D17S1185, D17S1144, D17S1145, EDH17B-A3T, EDH17B-DEL, D17S1147, D17S1142, D17S859, D17S858, D17S183, D17S579, D17S409, and D17S588. Markers were ordered by a combination of genetic recombination analysis (10), physical mapping by radiation hybrid analysis (18), fluorescent *in situ* hybridization (19), and PCR-based sequence-tagged site mapping of yeast artificial chromosome and cosmid contigs (20).

PCR amplification conditions were as follows: 10- μ L reactions contained 100 ng of genomic DNA, 2.5 pmol of each primer, 1.5 mM MgCl₂, 200 μ M each deoxynucleotide triphosphate, 50 mM KCl, 10 mM Tris (pH 8.3), 1 pmol [γ -³²P]-adenosine triphosphate (Amersham Corp., Arlington Heights, Ill.) end-labeled forward primer, and 1 U of Taq polymerase (Boehringer Mannheim Biochemi-

cals, Indianapolis, Ind.). The DNA was denatured for 4 minutes at 94 °C, followed by 35 cycles of amplification; each cycle consisted of 1 minute at 94 °C, 1 minute at the appropriate annealing temperature, and 1 minute at 72 °C. The amplified fragments were separated on 6% denaturing polyacrylamide gels and visualized by autoradiography (Kodak X-Omat, AR) for 3-12 hours.

Linkage Analysis

Linkage analysis was performed with the programs MENDEL (21) and LINKAGE (22). As previously described (9), an allele frequency of 0.003 was assumed for the dominant breast cancer allele. Individuals were assigned to one of seven age-related liability groups as determined by age of diagnosis or current age or age at death if unaffected. Unaffected males were assigned unknown disease status. Ovarian cancer cases were assigned to the affected-by-age-30 group because of the high likelihood of linkage to 17q for breast and ovarian cancer families (7). Liability classes were based on previously described segregation analyses (4).

DNA Extraction From Archival Samples

Samples of paraffin-embedded normal breast tissue were utilized as a source of DNA (9). Several 5-µm sections were cut from each paraffin block. Normal tissue was dissected from tumor tissue on each section. The paraffin was dissolved for 5 minutes in xylene and pelleted in 1:1, xylene:100% ethanol. Tissue pellets were dried and resuspended in 200 ng Proteinase K and 50 mM Tris (pH 8.3) per milliliter and incubated overnight at 37 °C. The samples were then boiled and used as DNA template in PCR reactions.

Results

The pedigree of family 15 is depicted in Fig. 1. The average age at onset of first malignancy (breast or ovarian cancer) in this family was 40 years. This family had previously generated a maximum 2-point LOD (i.e., logarithm of the odds) score of 1.58 at $\theta = 0$ with the marker D17S250 suggesting linkage between breast and ovarian cancer and markers flanking the BRCA1 locus (9). D17S250 is located approximately 1-2 cM

proximal to THRA1. Blood samples from 63 individuals, including eight affected by breast cancer (two of whom were also affected by ovarian cancer with age at onset between 30 and 55 years), were collected, and these individuals were genotyped. Seven of these breast cancer cases, including the two ovarian cancer cases, are presented in Fig. 1. Nineteen polymorphic DNA markers mapping to the BRCA1 region of chromosome 17q were screened on the family. In this article, data are presented from five markers (i.e., THRA1, D17S1139, D17S1185, D17S1147, and D17S579). These data indicate that an important recombination event is present in this family. The other 14 markers utilized in this study are described in the "Materials and Methods" section. Several individuals important for haplotype analysis of the family were dead. Three deceased affected individuals (IV-8, IV-2, and IV-15) were studied by use of paraffin-embedded normal breast tissue as a source of DNA. Genotypes of individuals for whom no DNA sample was available were inferred using genotypes of closely related family members.

Analysis of inferred haplotypes of individuals II-2 and II-7 suggests that a recombination event occurred in individual II-2. Individual II-2 was diagnosed with an aggressive, undifferentiated cervical cancer at 40 years of age and died of her disease at age 41. Confirmation of cervical cancer was obtained from the original pathology report and from re-examination of archival tissue. Individual III-2, a daughter of II-2, developed breast and ovarian cancers at ages 35 and 37, respectively, suggesting that both II-2 and III-2 inherited a disease allele of the BRCA1 gene. The haplotype of individual II-2 was inferred as follows: 1) The haplotype of individual II-7 was inferred with certainty, given the genotypes of individual II-8 and the descendants of II-7 and II-8. The haplotype of II-4 can be inferred in

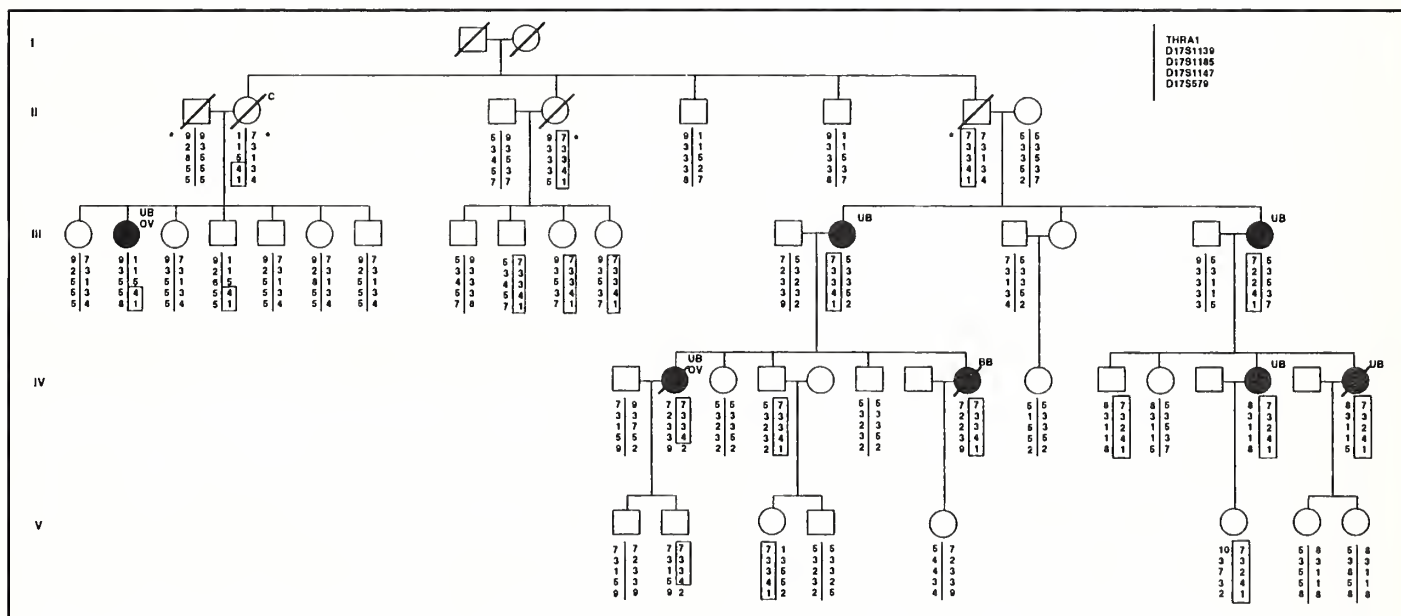


Fig. 1. Abbreviated pedigree of family 15 with associated most likely haplotypes. Some of the haplotypes shown above cannot be generated with certainty with the information provided (see text). A total of 15 markers from this region of chromosome 17q12-21 were informative in family 15. Five of these markers are presented above. The genotypes from these 15 markers allow the generation of the haplotype shown above as the most likely haplotype. C signifies cervical carcinoma, UB signifies unilateral breast cancer, BB signifies bilateral breast cancer, and OV signifies ovarian cancer. Boxed alleles represent the affected haplotype. Haplotypes for deceased individuals were determined by analysis of paraffin-embedded normal tissue when available. Inferred haplotypes are identified by an asterisk. Alleles are represented in code increasing from 1, the smallest allele, to the largest allele.

the same manner. 2) Using the genotypes of II-5 with II-6 and the haplotypes of II-4 and II-7, we can identify four parental generation 1 haplotypes. In addition, the haplotypes can be paired, but the pairs cannot be attributed to a specific parent. For this reason, the haplotypes of I-1 and I-2 are not shown in Fig. 1. 3) The seven progeny of individual II-2 provided sufficient information for generation of four haplotypes for II-1 and II-2 that cannot be attributed to either individual. 4) Comparison of these generation II haplotypes and genotypes and the possible haplotypes that can be inferred for individuals I-1 and I-2 suggests specific haplotypes for II-1 and II-2 and predicts that a recombination event occurred in individual II-2. The most probable disease-associated haplotype in individual II-2 was inherited distal from marker D17S1147, and the probable non-disease haplotype was inherited proximal from markers D17S1185 and D17S1139. This result places the recombination event in the D17S1185/D17S1147 interval and would have located the new proximal boundary of the BRCA1 candidate region at the marker D17S1185 flanking the D17S1185/D17S1147 interval.

Markers D17S1139, D17S1185, and D17S1147 have been localized on the physical map of the BRCA1 region (18). Other markers that are located between D17S1139 and D17S1147 were also typed on the family. However, these markers (D17S1144, D17S1145, EDH17B-DEL, and EDH17B-A3T) either were inferred as homozygous in individuals II-2 and II-7 or did not provide sufficient information to permit inference of haplotypes for these individuals.

A second recombination event in the family is seen in individual IV-2. This individual was diagnosed with breast cancer at age 30 years and with ovarian cancer at age 35 years. The recombination event was previously located between D17S579 and THRA1, which suggested that the BRCA1 locus was located proximal to D17S579 (9). The recombination event in this individual was verified by the identification of the recombinant chromosome in one of the patient's two sons. In the current study, haplotype analysis placed the recombination event between D17S183 and D17S579 (data not shown).

A spontaneous variation in the microsatellite marker D17S1185 was observed in individual III-17. This individual possesses a 2 allele for D17S1185. The parents of this individual did not possess a 2 allele. Haplotype analysis suggested that III-17 should have inherited a 3 allele. Three progeny of III-17 all inherited the 2 allele, suggesting that a spontaneous mutation of D17S1185 had occurred. Each DNA sample was typed in duplicate to verify genotyping.

Linkage analysis of 22 other breast and breast-ovarian cancer families was undertaken. Each family was typed with the markers THRA1, D17S579, and D17S409 from the chromosome 17q12-21 region. Analysis was performed as described in the "Materials and Methods" section. Eight families had a maximum 2-point LOD score of 1.18 or greater between the BRCA1 locus and at least one of the markers. Characteristics of families 15, 28, 30, 34, 46, 77, 130, and 178 are summarized in Table 1, and LOD scores for each marker are shown in Table 2.

Family 15 and the seven other families described above were screened for the presence of mutations within the coding region of the BRCA1 gene by use of the single-strand conformation polymorphism technique (14). A mutation was detected only in

Table 1. Characteristics of early-onset breast cancer families used for linkage analysis

Family	No. of individuals typed	No. of affected individuals typed*	Mean age at onset, y	No. of individuals with ovarian cancer
15	63	8	40.2	2
28	12	7	39.8	3
30	12	6	39.5	1
34	15	5	49.0	3
46	36	6	44.0	0
77	26	8	44.1	0
130	12	5	42.4	1
178	13	5	40.2	2

*Breast and ovarian cancers.

Table 2. Two-point LOD scores for early-onset breast cancer families and chromosome 17q markers

Pedigree	Recombination fraction					
	0.01	0.05	0.10	0.20	0.30	0.40
THRA1						
Family 15	1.53	1.40	1.26	0.97	0.65	0.32
Family 28	1.59	1.43	1.26	0.91	0.55	0.23
Family 30	1.01	0.89	0.76	0.50	0.26	0.09
Family 34	2.21	1.98	1.73	1.21	0.66	0.19
Family 46	1.77	1.57	1.37	0.98	0.58	0.22
Family 77	0.80	0.74	0.65	0.45	0.26	0.10
Family 130	1.18	1.04	0.90	0.60	0.31	0.09
Family 178	1.16	1.06	0.93	0.65	0.38	0.14
D17S579						
Family 15	0.40	0.85	0.90	0.77	0.51	0.22
Family 28	-0.83	-0.07	0.13	0.26	0.24	0.14
Family 30	1.63	1.46	1.28	0.92	0.55	0.20
Family 34	1.67	1.49	1.31	0.92	0.53	0.18
Family 46	2.02	1.86	1.68	1.27	0.80	0.31
Family 77	1.61	1.54	1.40	1.06	0.65	0.27
Family 130	1.18	1.04	0.90	0.60	0.31	0.09
Family 178	1.40	1.28	1.12	0.77	0.41	0.11
D17S409						
Family 15	1.89	1.71	1.53	1.13	0.71	0.30
Family 28	-0.58	0.33	0.47	0.46	0.34	0.17
Family 30	0.65	0.54	0.44	0.26	0.12	0.03
Family 34	0.31	0.27	0.24	0.15	0.07	0.02
Family 46	0.00	-0.01	-0.02	-0.02	-0.01	0.00
Family 77	1.46	1.41	1.30	0.97	0.58	0.23
Family 130	0.45	0.40	0.34	0.22	0.11	0.03
Family 178	0.00	0.02	0.03	0.01	-0.03	-0.04

family 15. A 4-base-pair (bp) deletion (3875del4) at nucleotide 3875 in the complementary DNA corresponding to codon 1252 resulted in a stop codon 29 bp downstream in a BRCA1 gene of family 15 (14). The mutation was tracked through the family to verify that the putative predisposing mutation segregated with the affected haplotype. The 4-bp deletion was detected in individual III-2 of family 15. The presence of the mutation indicates that this individual and her mother (II-2) did inherit a predisposing haplotype and that a recombination event did occur in II-2 between the markers D17S1185 and D17S1147, as suggested above. Furthermore, all individuals in possession of the predisposing haplotype in this family were found to have a 4-bp deletion.

Discussion

Prior to the identification of the BRCA1 gene, many families were analyzed for linkage between markers in the BRCA1 region and breast-ovarian cancers. Of particular interest were recombination events in linked families that could be used to reduce the size of the BRCA1 region. Family 15 was identified as one of eight apparently linked families in our collection. In this study, we describe the haplotype analysis of the BRCA1 region in an extended version of this pedigree. The analysis suggested the existence of a recombination event between the markers D17S1185 and D17S1147. This recombination event would have significantly narrowed the published BRCA1 interval (D17S857 to D17S78) that was in use when the BRCA1 gene was identified (12). The recombination event was thought to be uncertain, however, because the crossover was present in an individual unaffected by breast or ovarian cancer. This individual was diagnosed at age 40 with cervical cancer, which is not recognized as part of the syndrome. Both the original pathology report and archival histologic specimens from this deceased individual have been obtained, and the diagnosis of cervical cancer verified. It is possible that individual II-2 might have developed breast or ovarian cancer if she had not died at an early age from cervical cancer. This individual had one daughter (III-2) who developed both breast and ovarian cancers and who carries the associated haplotype. Three other daughters inherited the wild-type haplotype from their mother and are disease free at ages 56, 58, and 53 years. The early age of death at 41 years of individual II-2, along with the diagnosis of breast and ovarian cancers in her only daughter with a disease-associated haplotype, suggests that individual III-2 is unlikely to be a patient with a sporadic case of breast and ovarian cancer and that individual III-2 and her mother II-2 inherited a germline mutation in the BRCA1 gene. Unfortunately, evidence was insufficient at that stage to verify the recombination event and to eliminate the D17S857 to D17S1185 region from the search for the BRCA1 gene.

The haplotypes shown in Fig. 1 were generated with some difficulty. No sample was available for II-2, her spouse, II-1, or any of their parents. As a result of this lack of sample availability, the haplotypes for II-1 and II-2 had to be inferred from their offspring. No inheritance pattern for the haplotypes could be identified because of the lack of genotypes in the I and II generations. A comparison of haplotypes and genotypes from a number of related individuals was required to identify the most likely haplotype for individual II-2, as described above. It must be noted, however, that the recombination event is based on these reconstructed genotypes and haplotypes of individual II-2 and II-1. A total of 15 markers were informative in the family. The genotypes for each of these markers can be added to the proposed haplotypes without complication, again suggesting that the presented haplotype is the most probable haplotype.

The presented haplotypes of these individuals, however, are not the only possible haplotypes for this couple. The haplotypes of the founding parents, individuals I-1 and I-2, cannot be recreated with certainty. The two brothers, II-5 and II-6, provide genotype information, but not haplotype information. Individual II-4 supports the proposed haplotype; however, this individual

would appear to have possessed the affected haplotype but remained disease free until her death. Furthermore, both female offspring of II-4 (III-10 and III-11) also possess the putative disease haplotype but remain disease free at ages 53 and 65 years, respectively. For the proposed disease haplotype to segregate with the development of disease in this section of the family, individuals II-4, III-10, and III-11 must be considered members of the group of 15% of affected haplotype- and mutation-positive individuals who are nonpenetrant for early-onset breast-ovarian cancers. Clearly, had we not had mutation data, it would have been asked whether breast-ovarian cancers in this new section of family 15 are linked to the BRCA1 gene or are actually sporadic nonfamilial diseases. As a result of the large number of assumptions involved in validating the recombination event in this family, it was determined that this recombination event did not provide solid enough evidence to reduce the size of the BRCA1 interval.

Following the cloning of the BRCA1 gene (13), mutation studies were performed on a large number of early-onset breast-ovarian cancer families. Of particular relevance to this study was the identification of a mutation in the BRCA1 gene of family 15 members. The mutation 3875del4 was shown to cause a frameshift and results in the truncation of the BRCA1 protein. This truncation is presumed to cause a loss of function of BRCA1. The mutation was also shown to track with the disease haplotype in the family. In fact, it was demonstrated that the mutation was present in III-2, indicating that individuals II-2 and III-2 did possess the disease haplotype and that a recombination event was present in II-2 in the previously described BRCA1 region. Furthermore, individuals III-10 and III-11 and, by inference, their mother (II-4), though unaffected, were shown to possess the familial BRCA1 mutation. The presumptions made in the genetic analysis study were all validated by the detection of this mutation. However, even though the original analysis has been shown to be accurate, this result in no way changes the uncertainty with which a similar situation in another family would be viewed.

We believe this finding illustrates some of the problems that can be encountered during genetic analysis of cancer families. Here was a large, informative pedigree with a potentially important recombination event that had to be viewed with skepticism because 1) a number of individuals with the putative disease haplotype were unaffected and 2) samples from key individuals were unobtainable because of the high number of deaths resulting from cancer in younger individuals. Many families who might have proved useful for the isolation of cancer predisposition genes have been rendered uninformative because of these two major obstacles.

Linkage analysis was performed on an additional 22 breast-ovarian cancer families. Seven of these families had maximum 2-point LOD scores in excess of 1.0 for at least one marker flanking BRCA1. A negative LOD score of -0.83 at $\theta = 0.00$ for the D17S579 marker in family 28 suggests that at least one recombination event exists between BRCA1 and D17S579 in this family. This result was confirmed by haplotype analysis. Mutation analysis was also performed on the seven families (14); however, no mutations were identified. There are several reasons why mutation analysis may not support linkage analysis

results. These families were considered tentatively linked to BRCA1, given the LOD score greater than 1.00. An LOD score of 1.00 is by itself only very limited evidence for linkage, however, and does not rule out the possibility that breast-ovarian cancers in these families may appear to be linked only to BRCA1 and may actually be linked to another breast cancer susceptibility gene. Clearly, no mutations would be detected in the BRCA1 gene in those families who are linked to other loci. Moreover, the BRCA1 gene in these families was screened by the single-strand conformation polymorphism technique using PCR products, many of which were greater than 250 bp (14). Products of this size are thought to result in a mutation-detection efficiency of only 60%-70%. Many mutations may thus remain undetected. Finally, the mutations in the BRCA1 gene in these families may be present in the promoter, deep in the introns or in the 3' untranslated regions of the gene. The single-strand conformation polymorphism analysis that was performed on these families was limited to the coding region of the gene. These possibilities may account for the seven mutations in the seven apparently linked families that have not been determined. The BRCA1 complementary DNA in each of these families is currently being directly sequenced in a further attempt to locate the putatively overlooked mutations.

Despite these problems, the importance of identifying new families with apparent autosomal dominant inheritance of breast cancer cannot be understated. New families can now be screened for the presence of BRCA1 mutations, which will add to our ability to determine structure-function relationships within the BRCA1 gene and to accurately identify women who are at high risk of developing breast and ovarian cancers as a result of BRCA1 germline mutations. In addition, families without evidence of BRCA1 mutations can be studied as a means of localizing and isolating additional breast cancer-related genes. Every new family has the potential to help in the identification of or assist in narrowing the size of a candidate interval for additional breast cancer genes by identification of new meiotic recombination events between flanking markers and the disease locus.

Genetic diagnosis of individuals in family 15 is now possible. All eight affected individuals have been shown to carry the germline BRCA1 mutation. The remainder of the family contains eight living, unaffected females possessing a BRCA1 mutation and 12 living male carriers of the mutation. Only five of these males and four females are represented in the abbreviated pedigree shown in Fig. 1. These individuals and their progeny can now be closely monitored for the development of component tumors. The other family members can be assured that their risk of developing cancer remains that of the general population, and the very high risks associated with BRCA1 mutations do not apply.

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A 45-Year Follow-up of Kindred 107 and the Search for BRCA2

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Interest in the genetics of breast cancer has intensified with the discovery of a breast cancer susceptibility locus, BRCA1, on chromosome 17q. In this paper, we describe updated information on a large breast cancer kindred (K107) that has been extensively studied since 1948. Specifically, we have identified many new cases of cancer in the family and have shown that this family is unlinked to BRCA1 as well as a number of other genes considered as candidates for breast cancer. In a collaborative study between the University of Utah and the Institute of Cancer Research in the United Kingdom, we have collected a set of families with a predisposition to breast and ovarian cancers that have been reliably excluded from linkage to BRCA1 and evaluated their usage in a genomic search for other breast cancer loci. This effort led to the discovery of a second breast cancer locus located on chromosome 13q, BRCA2, which is responsible for the increased incidence of breast cancer in Kindred 107. [Monogr Natl Cancer Inst 17:15-19, 1995]

Although a state with a relatively small population base, Utah has proven to be an excellent location for studying genetic predisposition to common disease. This is due, in part, to polygamy practiced among the Utah pioneers and to the emphasis of the Church of Jesus Christ of Latter-day Saints ("Mormon") on large families and the maintenance of genealogical records. This genealogical resource has been linked to the Utah Cancer Registry (UCR) and other public records to form the Utah Population Database. This resource facilitates the identification and analysis of families with apparent genetic predisposition to cancer. One such family, Kindred 2082, contains 35 cases of breast or ovarian cancer due to the BRCA1 gene and has been recently studied in detail (1). The focus of this paper, however, is on families whose predisposition to breast cancer is not due to BRCA1. In particular, we will present an update on one such unlinked kindred (K107), which contains 47 cases of breast or ovarian cancer, and discuss our strategy for localizing additional genes that confer susceptibility to breast cancer.

Perhaps the earliest large kindred with an apparent inherited susceptibility to breast cancer was that reported by Gardner and Stephens (2) in 1950 and identified as Kindred 107 (K107). This family was originally ascertained in 1947 by a University of Utah genetics student with two great-aunts who died of breast cancer in their 40s. Subsequent clinical and genealogical follow-

up identified seven additional cases of breast cancer and many benign breast tumors. The family was updated several times, most notably in 1980 (3). In a study by Bishop and Gardner (3), 22 new cases of breast and ovarian cancers were identified and the penetrance of the gene was estimated to be 0.82 by age 80. More recently, we have attempted to update the cancer status of all members of the kindred and to explore cancer incidence in new branches of the family. This task was somewhat complicated because, although much of the family remains in the Salt Lake valley, parts of the family are scattered across the western United States and Canada. More important, attempts were made to obtain blood samples from a large number of affected women and their relatives in K107. The kindred is now known to contain 38 cases of female breast cancer, three cases of male breast cancer, and six cases of ovarian cancer. Fig. 1 shows a reduced pedigree drawing of K107 showing the temporal identification of cases, while Table 1 shows the distribution of age at diagnosis of the breast and ovarian cancer cases in K107. We were able to obtain histology coding from the UCR or from medical records for 18 of the cases shown in Table 1 and Fig. 1. Of these cases, 11 were coded as infiltrating ductal, four were adenocarcinoma (not otherwise specified), one was intraductal papillary carcinoma, and one was a case of Paget's disease.

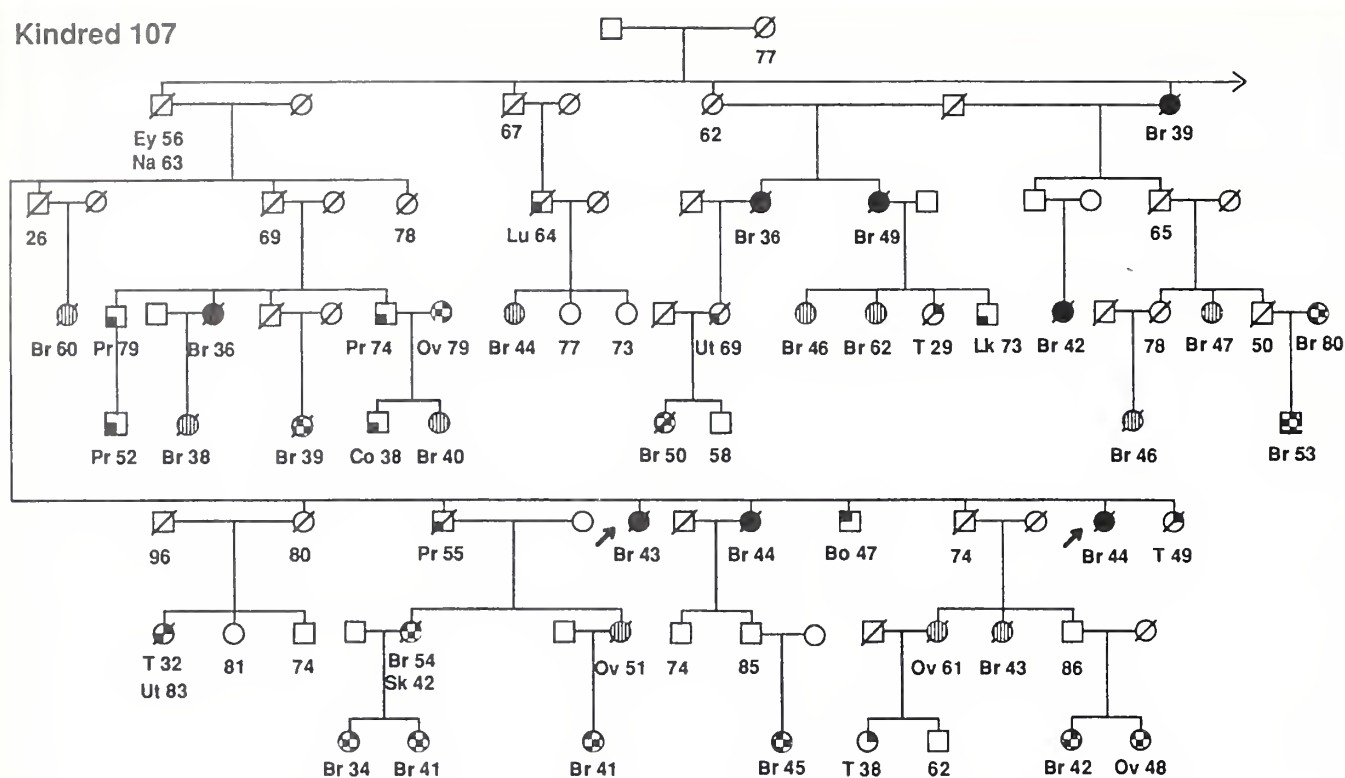
Although at this stage we have not formally re-estimated the penetrance of the gene responsible for the breast cancer in K107, examination of the status of obligate carriers (i.e., connecting parents of cases) in Fig. 1 demonstrates that the hypothesized locus is highly penetrant. The phenotypic status of obligate carriers is shown in Table 2. As one would expect, the vast majority of the female obligate carriers were affected with cancer or benign premalignant lesions; however, it is noteworthy that eight of the 17 male obligate carriers who survived until at least age 55 developed a malignancy. Conspicuously, four obligate carriers developed prostate cancer at ages ranging from 55 to 80 years. A number of other cancers appear to be associated with the expression of this gene, most notably prostate

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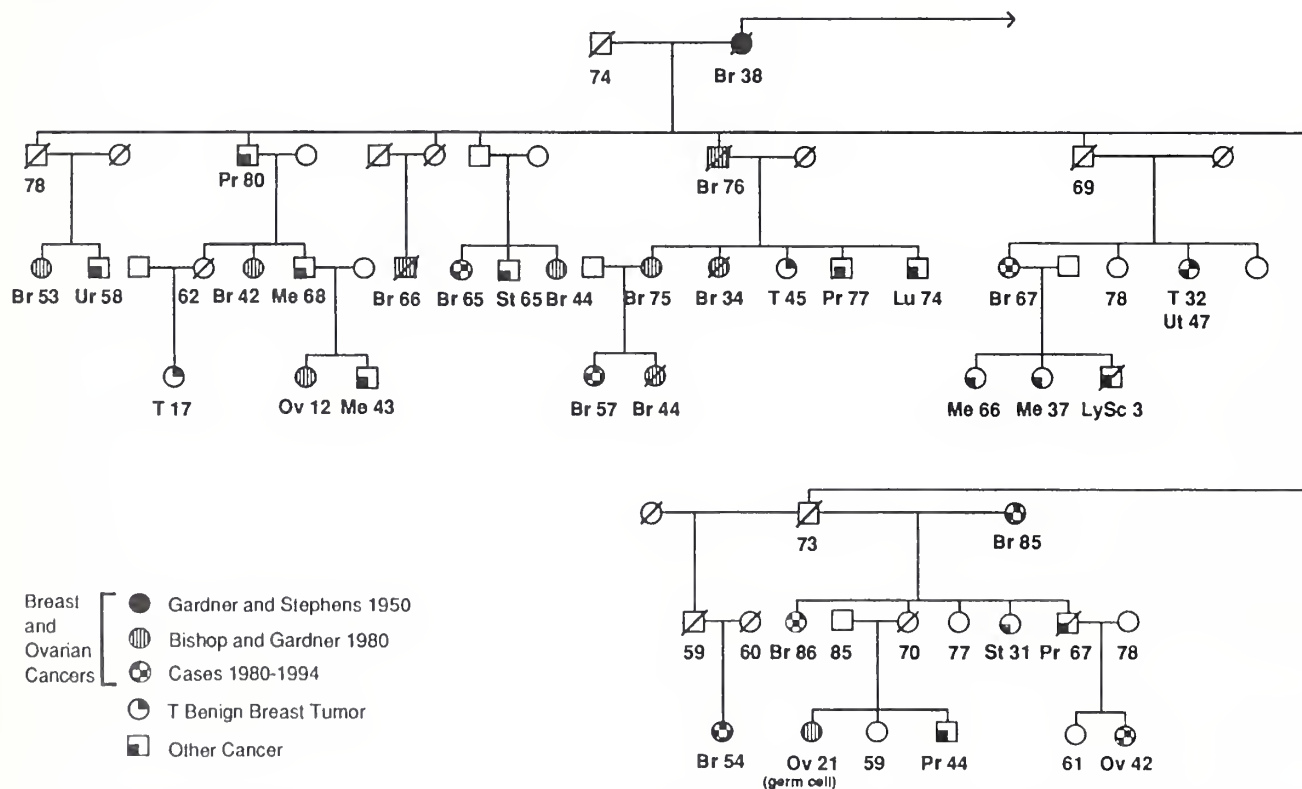
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See "Notes" section following "References."

Kindred 107



Kindred 107



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Table 1. Age at diagnosis of K107 breast and ovarian cancers*

Cancer	Age at diagnosis, y			
	≤40	40-49	50-59	≥60
Breast	8	17	7, M	6, M, M
Ovarian	2	2	1	1

*M = male breast cancer.

Table 2. Cancers at other sites in relatives of breast and ovarian cancer cases*

Site or type	First-degree relatives		Second- and third-degree relatives	
	No.	Ages at diagnosis, y	No.	Ages at diagnosis, y
Prostate	6	44, 55, † 67, † 74, 75, † 80†	1	52
Uterus	3	44, 70, † 82‡	1	47‡
Melanoma	2	43, 72	3	37, 66, 68†
Navel	1	63†		
Eye	1	56†		
Bone	1	47	1	7§
Colon	1	38	1	68§
Urethra	1	61		
Basal cell	1	41‡		
Lip			1	64§
Lymphoma	1	56		
Lung	2	64, † 74		
Leukemia	1	73		
Lymphosarcoma			2	3, 9§
Osteosarcoma			1	12§
Throat			1	49§
Stomach			1	31
Thyroid			1	9§

*Only relatives of breast cancer patients diagnosed under age 60, male breast cancer, or ovarian cancer are listed.

†Cancer found in an obligate carrier of a presumed susceptibility locus.

‡Second cancer in a woman with breast or ovarian cancer.

§Third-degree relative; all others are second-degree.

cancer, melanoma, and uterine cancer, as shown by both the obligate carriers and in the cancers found in relatives of affected women in the family (Table 2). Interestingly, population-based studies of familial cancer have shown possible familial associations between breast and prostate cancers (4) and breast, prostate, and uterine cancers (5,6).

After obtaining a sufficient number of DNA samples, studies were undertaken to identify the gene responsible for the unusual cluster of breast cancer cases in K107. A natural place to start such a search, of course, is the BRCA1 gene for familial breast and ovarian cancers on chromosome 17q (7-9).

Linkage to the BRCA1 region was investigated in this kindred by genotyping four markers that cover the region known to contain BRCA1. Linkage to BRCA1 could be reliably excluded in K107 based on the analysis of the 17q marker typings. In addition to the negative logarithm of the odds (LOD) scores with 17q markers shown in Table 3, at least 10 distinct 17q

BRCA1-region haplotypes were observed among breast cancer patients diagnosed under age 50, male breast cancer, or ovarian cancer. In addition, a series of other loci that could be considered to be candidate regions or candidate genes for breast cancer were tested and similarly excluded (Table 3). These included regions defined by loss of heterozygosity in breast or ovarian tumors, loci involved in familial cancer at other sites, or loci for which some evidence of involvement in familial breast cancer has been previously reported.

The phenotypic pattern of cancer observed in K107 does not appear to be an isolated occurrence. A systematic survey was undertaken to identify all families containing at least one case of male breast cancer, at least two cases of female breast cancer diagnosed under the age of 50, and one or more cases of ovarian cancer (designated "BMO" families). In collaboration with M. Stratton at the Institute of Cancer Research (ICR), a set of 12 such families were collected together with 10 families that met the above description but did not have any cases of ovarian cancer (10). Based on genotypings for markers surrounding BRCA1, no evidence for BRCA1 linkage was found. The best estimate of the proportion of families linked was zero, with an upper 95% confidence limit of 20%.

To localize the breast cancer susceptibility locus in these families, as well as in other breast cancer families unlinked to BRCA1, a collaboration was formed between the ICR and the University of Utah. Initially, a set of 22 families, consisting of five of the most informative of the BMO families, five unlinked breast and ovarian cancer families without a male case, and 12 families with early-onset female breast cancer only were examined to determine their power for localizing additional breast cancer loci under a variety of situations. As detailed below, simulation studies using the program SLINK (11) showed this set to contain sufficient power to localize one or more breast cancer susceptibility loci, even if further genetic heterogeneity is present.

Assumed Model for Candidate Gene Tests

Since in this case we are testing a specific-candidate gene, we assumed in the simulations that we had a polymorphic marker

Table 3. Linkage analysis of chromosome 17q markers and candidate regions in K107

Chromosome 17q markers		LOD scores	
Locus		$\theta = 0.001$	$\theta = 0.05$
THRA1		-2.22	-0.47
D17S855		-3.03	-1.55
D17S1325		-2.43	-1.70
D17S1184		-3.57	-2.14
Gene/region		Candidate locus for breast and ovarian cancers	
		LOD ($\theta = 0.01$)	
p53	D17S796		-2.47
Estrogen receptor	ER6		-2.55
CAR/16q	D16S413		-2.99
MTS1/MLM	CT29		-3.37
MSH2	D2S123		-1.55
Mlh1	D3S1289		-1.58

within the gene complex of interest or, alternatively, close-flanking markers surrounding the gene. Accordingly, we assumed for these simulations a recombination fraction of 0.001 between the disease and a marker locus assumed to have five equally frequent alleles. The model for the disease gene was assumed to be that described in a study by Easton et al. (9). Because it is unlikely that any single-candidate gene would be responsible for all non-BRCA1 familial breast cancer, we also conducted the simulations under an assumption that, on average, 50% of the families would be linked to a given candidate locus.

Assumed Model for Genomic Search

In this case, we assume that we have flanking markers each located 10 cM (centimorgan) from the hypothesized disease locus. To ensure that an adequate number of replicates could be simulated in a reasonable amount of computer time, we modeled two flanking 4-allele markers as a single locus with 10 equally frequent alleles, located 9 cM from the disease. On small pedigrees, these two models have roughly equivalent information content; we assumed that this was also the case for the larger pedigrees. Again, we simulated linkage homogeneity and 50% heterogeneity.

The studies described above demonstrated that our set of families have more than adequate power if there is only minimal further heterogeneity (in addition to BRCA1) or if the genetic heterogeneity is accounted for largely by our phenotypic classification. It seems likely that the BMO classification is a genetically homogeneous subset. If heterogeneity is present throughout the family material and is of the order of 50%, we have shown that we still have a reasonable chance (65%) of detecting linkage to a breast cancer susceptibility locus. If the degree of genetic heterogeneity is higher, it may still be possible to detect linkage to one or more susceptibility loci, since we have several individual families in our set, each of which is capable of achieving a LOD score greater than 3.0.

The Search for BRCA2

As a first step in identifying additional breast cancer susceptibility loci, linkage between breast cancer and the candidate loci shown in Table 3 was tested in a combined set of 15 families. Each of the candidate loci could be excluded from playing a significant role in the breast or ovarian cancer in these families. Initially, 200 markers spaced at roughly 20-30 cM across the genome were examined for linkage in the University of Utah and ICR families. When no significant evidence of linkage was found to any of these initial markers, a second set of markers from the newer Genethon set (12) was used to fill in the gaps in the previous set and to cover areas of the genome that were not excluded. During the course of this latter analysis, a hint of linkage was found to D13S260 in the ICR families, and this was subsequently confirmed in the University of Utah set of families. In all, 15 families were analyzed for five markers on chromosome 13q. A maximum multipoint LOD score was found between breast and ovarian cancers and D13S260/D13S67 of 9.58, with significant evidence of genetic heterogeneity (13). This locus was denoted BRCA2. An estimated 74% of the

families were linked to BRCA2; the LOD score under heterogeneity was 11.65. Among the families that showed convincing evidence of linkage to 13q was K107, which had a multipoint LOD score of 3.48 (13). Interestingly, although K107 did have six cases of ovarian cancer, four of these cases did not carry the linked 13q haplotype. Thus, the role of BRCA2 in ovarian cancer remains uncertain.

Conclusion

K107 may be representative of a new familial cancer syndrome consisting of early-onset female breast cancer, ovarian cancer, at least one case of male breast cancer, and, possibly, prostate cancer, uterine cancer, and melanoma. Linkage analysis has shown that the gene responsible for K107 and the majority of families with a similar phenotype is located on chromosome 13q. Prospective follow-up of K107 will continue to provide useful information on the penetrance of the susceptibility locus and its associations with cancers at other sites. This effort will now be facilitated by the presence of a linked haplotype that will allow more precise estimation of the effects of the BRCA2 mutation segregating in K107. Although most breast cancer and breast and ovarian cancer families appear to be due to either BRCA1 or BRCA2, a number of high-penetrant, early-onset families are inconsistent with linkage to both BRCA1 and BRCA2, indicating the presence of one or more additional breast cancer loci. The collaboration between the University of Utah and the ICR is continuing to search the genome, with the goal of identifying these additional loci.

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Genomic Imprinting, DNA Methylation, and Cancer

*Andrew P. Feinberg, Shirley Rainier, Michael R. DeBaun**

Our basic concepts of segregation and assortment of two alleles of a gene have been shaped by the work of Mendel (1) near the beginning of this century. Similarly, our notions of genetic disorders were set more than 75 years ago by Garrod (2), who distinguished patterns of inheritance that depended on whether one or both copies of a gene are needed for normal function. There are two important assumptions implicit in Mendelian models of genetic inheritance: 1) that the maternally and paternally inherited alleles of a gene are identical, and 2) that two working expressed copies of a normal gene are always associated with normal function. Genomic imprinting challenges both of these assumptions.

Genomic imprinting is formally defined as a modification that causes differential expression of maternally and paternally inherited copies of a gene (3). The nature of this modification is unknown but must: 1) involve the gene itself or the chromosome on which it resides, 2) occur early in development (gametogenesis) or shortly after fertilization, 3) be heritable by somatic cells during cell division, and 4) be potentially reversible, since the imprint can be changed during reproduction of the organism.

Genomic imprinting has been known to exist in lower organisms for many years, but it has attracted great excitement recently because it is now known to be essential for normal development, and because a molecular mechanism, DNA methylation, has been tentatively identified. While there had been reasons to suspect that imprinting was important for human genes as well, only recently has molecular evidence for imprinting been reported in humans (4-8). Recent data (9,10) have linked altered DNA methylation to abnormal imprinting in cancer, and a transgenic animal model strongly supports a role for altered imprinting in progression of adenoma to carcinoma (11,12).

Evidence of Genomic Imprinting in Other Species

The greatest insight into mammalian imprinting comes from several lines of experimentation in mice. First, androgenetic embryos (with two complete paternal chromosomal complements) fail to develop normal embryonic tissues (13), while parthenogenetic embryos (with two complete maternal chromosomal complements) fail to develop extraembryonic tissues (13,14). These experiments demonstrate that maternal and paternal genomic complements are necessary for normal embryonic development. Second, mice harboring certain balanced translocations that result in uniparental disomy (chromosomal regions in which both copies are derived from a single parent) develop growth and developmental abnormalities (15). A direct relationship of imprinting to the regulation of cell growth is suggested

by the fact that for some chromosomal regions, paternal uniparental disomy leads to increased growth and maternal uniparental disomy leads to decreased growth (16). These findings have led to the hypothesis of Moore and Haig (17) that suggests that imprinting evolved because of opposing paternal and maternal interests in the growth of the embryo. These studies have also provided important mapping data for imprinted regions in the mouse, and by virtue of comparative mapping have suggested potentially imprinted regions in humans as well.

Work on transgenic animals, which contains a stably integrated foreign gene, has provided further evidence of imprinting. Some transgenes are only expressed when inherited from a specific parent (18). This imprinting of the transgene is also associated with specific differences in DNA methylation between the active and imprinted (inactive) alleles (19,20), thus suggesting a role for DNA methylation in the control of imprinting. DNA methylation is the enzymatic addition of a methyl group to the 5 position of the cytidine ring in genomic DNA by DNA methyltransferase. Other examples of imprinting include the preferential inactivation of the paternal X chromosome in kangaroos and other marsupials (21) and in the extraembryonic tissue of rodents (22).

Finally, there is direct molecular evidence of imprinting of several mouse genes, including the insulin-like growth factor-II gene (IGF2), expressed only from the paternal allele (23,24); H19, expressed only from the maternal allele (25); the Igf2 receptor gene (Igf2r), expressed only from the maternal allele (26); and Snrpn (small nuclear ribonucleoprotein-associated polypeptide SmN), expressed only from the paternal allele (27,28).

Evidence of Genomic Imprinting in Man

Compelling evidence of genomic imprinting in human disease comes from two disorders that show uniparental disomy. Prader-Willi syndrome (PWS) involves either maternal uniparental disomy for band 15q11-12 or visible cytogenic deletion of the same region from the paternal chromosome (29). PWS is

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See "Notes" section following "References."

characterized by short stature, mental retardation, and uncontrolled appetite leading to massive obesity. A second disorder, Beckwith-Wiedemann syndrome (BWS), involves paternal uniparental disomy of 11p15 in some patients. Other patients with BWS show balanced rearrangements involving the maternally inherited chromosome or duplication of the paternal chromosome. The genetics of both PWS and BWS imply that the maternal and paternal alleles of those genes are expressed differentially in normal development and that the disorder arises from an abnormal dose of these genes (either decreased or increased). Several imprinted genes have been isolated in the region of deletion in patients with PWS at 15q11-12, including SNRPN. This gene is a small nuclear RNA molecule that is maternally expressed in mice (27). The location and imprinting of SNRPN suggest a role for this gene in PWS, although mutations in the gene have not yet been found. A second disorder of chromosome 15, Angelman syndrome, also appears to involve an imprinted gene. Angelman syndrome is characterized by severe mental retardation and a characteristic movement disorder, and, in this case, loss of maternal rather than paternal DNA. The affected region is near to, but distinct from, the PWS locus.

The existence in mice of several imprinted genes, *Igf2* and *H19*, in the region of mouse chromosome 7 homologous to the human BWS region (11p15) has suggested a role for these genes in this syndrome (30). Moreover, genomic imprinting of these two genes in humans has recently been demonstrated directly in our laboratory (4) and in other laboratories (5-8) by examining RNA from a variety of tissues. Messenger RNA was reverse transcribed into complementary DNA, amplified using PCR, and digested with a restriction enzyme that recognizes a transcribed polymorphism to determine which parental allele was expressed. *Igf2* was expressed from the paternal allele and *H19* was expressed from the maternal allele (4-8). Several hereditary diseases, including Huntington disease and Fragile X syndrome, show variable penetrance depending on the parent from whom the gene is inherited, implying a role for imprinting in the disease process. However, at least in the case of Fragile X syndrome, the two parental alleles are not known to be differentially expressed normally, rather, the maternal allele is more susceptible to lengthening of an already mutant long trinucleotide repeat in the coding sequence of the gene. This differential allele mutability, while loosely referred to as a form of imprinting, does not represent differential allele expression as defined in other organisms.

Alterations in Genomic Imprinting in Human Cancer

The potential role of genomic imprinting in human cancer is suggested by several lines of evidence. Two unusual human tumors appear to arise from an abnormally imprinted genome. Hydatidiform mole, a uterine mass of cysts resembling a cluster of grapes, arises from a totally androgenetic genome, i.e., 46 chromosomes from the father (31). Conversely, complete ovarian teratoma, an unusual tumor that presents as an ovarian cyst often containing teeth and hair, arises from a totally parthenogenetic genome, i.e., 46 chromosomes from the mother

(32). Additional evidence of imprinting in cancer comes from hereditary cancer syndromes, such as hereditary paraganglioma, which is inherited exclusively from the father (33), and possibly familial adenomatous polyposis (FAP), which may show a preference for paternal inheritance (34).

Another major line of evidence is the preferential involvement of a specific parental allele in loss of tumor suppressor genes. Molecular evidence of the loss of specific tumor suppressor genes comes from a decade of observations beginning with two childhood tumors, Wilms' tumor and retinoblastoma. These tumors frequently show loss of heterozygosity (LOH) of polymorphic markers on specific chromosomal arms. For example, in Wilms' tumor, using restriction fragment length polymorphisms that distinguish the maternal and paternal chromosomes, one frequently finds LOH or loss of one of the polymorphic markers in a tumor of 11p, indicating that the chromosome arm has been lost and that it contains a tumor suppressor gene that has also been lost (35). Subsequently, LOH has been found in a wide variety of common tumors and has led to the localization and eventual cloning of a series of important tumor suppressor genes, such as *DCC* and *FAP* in human colorectal cancer (36,37). Interestingly, several neoplasms have shown LOH that preferentially involved a specific parental allele. For example, maternal chromosome 13 was lost in sporadic osteosarcoma (38); paternal chromosome 7 was lost in acute myelogenous leukemia (39); and maternal chromosome 11 was lost in Wilms' tumor, rhabdomyosarcoma, and hepatoblastoma (40). Chronic myelogenous leukemia also shows indirect evidence of genomic imprinting in carcinogenesis. The Philadelphia chromosome translocation was shown to involve both the paternal chromosome 9 and the maternal chromosome 22 exclusively (41). However, the *bcr* gene on chromosome 2 is not imprinted (42).

The first direct evidence that abnormally imprinted genes may play a role in tumorigenesis was found by examining imprinting of *Igf2* and *H19* in Wilms' tumors. Rainier et al. (4) and Ogawa et al. (6) observed that in normal kidneys, the paternal allele of *Igf2* is expressed and the maternal allele is transcriptionally inactive. In Wilms' tumors, 70% of the tumors show loss of imprinting (LOI), expressing both the maternal and paternal alleles. LOI was present in the earliest stage of tumors as frequently as in later-stage tumors. Moreover, we found that LOI of *H19* also occurs in these tumors but at a lower frequency (<20%). *H19* is a gene that apparently encodes an RNA of unknown function (43). LOI has now been seen in several other tumor types, including rhabdoid tumor (4), rhabdomyosarcoma (44), adrenocortical carcinoma (45), and testicular cancer (46).

DNA Methylation as a Mechanism of Altered Genomic Imprinting in Cancer

Alterations in the methylation of genes in cancer were first described more than 10 years ago by Feinberg and Vogelstein (47). Recent data suggest that these changes may play a critical role in disturbed imprinting in cancer. In mice, methylation appears to mark, or imprint, a paternally specific allele of two imprinted genes. A CpG island (or domain of CG-rich sequence) is specifically methylated on the paternally inherited (unex-

pressed) H19 (48); a CpG island is also methylated on the maternally (expressed) Igf2R allele (26). The parental origin-specific methylation is not linked to tissue-specific gene expression, as in most DNA methylation, but to parental origin, as predicted for an imprint. Furthermore, DNA methyltransferase-deficient knockout mice lacking methylation of these CpG islands lose imprinting of the affected genes (49). With these data in mind, we compared tumors with LOI to those without LOI. Strikingly, LOI of IGF2 always involved complete methylation of this island on the maternal chromosome. Thus, the maternal chromosome was always associated with loss of expression of H19 on the same (maternal) chromosome and activation of the IGF2 gene (as on the paternal chromosome). Furthermore, in all Wilms' tumors examined, LOI involved abnormal methylation of the imprint-associated CpG island on this chromosome. Thus, LOI involves a switch of the maternal chromosome to a paternal epigenotype (9,10).

Potential Effects of LOI on Cancer Cells

Since retinoblastoma provided a tangible illustration for the two-hit hypothesis of Knudson and Strong (50) for tumor suppressor genes, loss of imprinting in cancer may introduce a new paradigm for carcinogenesis. What might be the potential effects of loss of imprinting in cancer? The most obvious potential effect is an increase in expression of the gene that has undergone LOI, namely, from one copy to two copies of the expressed gene. Many other genetic alterations in cancer can cause abnormal expression of normal cellular genes, such as DNA amplification of N-myc in neuroblastoma (51) and MDM2 in sarcoma (52) and translocation of c-myc in Burkitt's lymphoma (53,54). LOI of IGF2 could be an important step in carcinogenesis by causing increased levels of IGF2. That such a gene activation mechanism may be important is suggested by the role of IGF2 as an important autocrine growth factor in a wide variety of tumors, including lung (55-57), breast (58,59), colon (60-63), thyroid (64), liver (65,66), and brain (67,68). Indeed, the blockade of IGF2 by suramin at the insulin-like growth factor 1 receptor [IGF1R, the receptor that carries out the growth function of IGF2 (69)] causes growth inhibition in vitro of human rhabdomyosarcoma, and clinical trials are under way to inhibit IGF2 at its receptor in rhabdomyosarcoma (70). Direct support for this model comes from studies of transgene-induced liver tumors, which require activation of both IGF2 alleles for complete progression from adenoma to carcinoma (11,12). In Wilms' tumor, one proposed mechanism for the activation of IGF2 is mutation of the WT1 gene on 11p13, a transcriptional repressor of IGF2 and other genes (71). However, the frequency of mutation of WT1 in Wilms' tumor is less than 10% (72). Thus, LOI may be a more common change leading to deregulated expression of IGF2 in Wilms' tumor.

An alternative mechanism, first suggested by Sapienza (73), is that abnormal imprinting could inactivate one copy of a tumor suppressor gene. Thus, preferential LOH may be due to abnormal imprinting and inactivation of the retained allele during early embryogenesis (74). If the lost gene is a tumor suppressor gene, its inactivation may lead to cancer. For example, if H19 is a tumor suppressor gene, as is suggested by the recent report

(75), loss of the maternal allele in Wilms' tumors would cause loss of the active copy of H19 and presumably decreased H19 levels.

A third potential mechanism is a more complex interaction between neighboring loci that are reciprocally imprinted. At least in the case of IGF2 and H19, one gene is expressed from the paternal chromosome and the other is expressed from the maternal chromosome. Thus, a change in imprinting of either gene could affect the expression of the other. In mice, IGF2 and H19 map to a region of less than 90 kb, and thus a regulatory domain lying between them may act as an allele-specific switch controlling the exclusive expression of IGF2 or H19 (76). Thus, a common final pathway of LOH and LOI may be decreased expression of H19. Regardless of the mechanism, LOI would be expected to lead to abnormal expression of imprinted genes in the cancer cell.

Another proposed mechanism for maintenance of imprinting comes from *Drosophila* studies of heterochromatin (77), transcriptionally silent regions of the *Drosophila* genome, by virtue of its folding into a tight complex with specific proteins. A number of the protein components essential for heterochromatin formation in *Drosophila* are known. A normally active gene, when translocated next to heterochromatin, can be transcriptionally silenced. This silencing is heritable. When one of the factors necessary for heterochromatin formation is limiting, it affects the scope of heterochromatin formation and can release transcriptionally silenced genes from the silencing effects of heterochromatin (78). Increasing the expression of this limiting factor can also increase the scope of heterochromatin formation and repress neighboring genes that are normally expressed in the cell. Therefore, there is a critical concentration of these factors necessary to maintain heterochromatin and thus the normal expression of genes in these cells. One can envision an analogous mechanism in humans, although there is no direct molecular evidence that these factors exist in humans. These observations in other organisms help to predict models and design experiments to explain the mechanism of imprinting in humans.

Recent work (79) examining replication timing in imprinted genes indicated that there are large domains surrounding imprinted genes that show early replication of the paternal allele. Unimprinted genes located within these domains are also late replicating, and later replication of the paternal allele does not correlate with allele-specific expression of the imprinted genes. For example, H19 and IGF2 are expressed from different alleles yet show early replication of the paternal allele. Therefore, the authors suggest a more complex mechanism for allele-specific expression involving local transacting factors. Finally, another possible mechanism for imprinting derived from studies in yeast is gene conversion. In yeast, gene conversion plays a role in controlling mating type (80). The region of the yeast genome that controls mating type contains two genes separated by a control or "switch" region. Only one of these genes is active in a cell, but a daughter cell can switch mating types by inactivating the active gene and activating the inactive gene. The daughter cell can then pass on the new phenotype to its progeny.

Implications of Altered Genomic Imprinting to the Genetic Epidemiology of Cancer: BWS as a Model

Our laboratory suspected several years ago that BWS may involve altered genomic imprinting because we had mapped the gene to 11p15.5 by genetic linkage analysis in families (87); this region is homologous to a known imprinted region of mouse chromosome 7. In particular, mice with maternal isodisomy of chromosome 7 are small compared with their expected size (82); whereas mice with paternal isodisomy have increased growth of the mouse embryo (48). BWS is characterized by dramatic overgrowth, high birth weight, macroglossia, and organomegaly. Both enlarged liver and kidneys are predisposed to the development of hepatoblastoma and Wilms' tumor, respectively. Thus, in patients with BWS, there appears to be increased stimulation of growth in selected tissues that may lead to tumor formation.

A further clue in the role for imprinting in BWS was the discovery by Henry et al. (83) of paternal uniparental disomy in BWS. The involved region includes that linked to BWS in families studies (11p15.5). This band also harbors the IGF2 gene, which we found to be paternally expressed in normal tissues, with LOI in cancer, including tumors to which BWS patients are susceptible. Several laboratories have found direct evidence of altered imprinting in BWS with LOI of IGF2 in nonmalignant tissue. Furthermore, Steenman et al. (9) and Moulton et al. (10) have shown that nonmalignant BWS tissues may display the same pattern of reversal of chromosome-specific imprinting seen in sporadically occurring tumors. Thus, the maternal chromosome exhibits expression of IGF2, downregulation of H19, and a paternal pattern of methylation of the imprint-specific CpG island in the H19 promoter.

We believe that the alterations in IGF2 reflect a more generalized disturbance of imprinting on chromosome 11, because LOI of IGF2 occurs in only about 20% of tumors. Furthermore, balanced germline translocations of chromosome 11 in BWS patients are all of maternal origin, suggesting loss of maternal imprint induced by the translocation (Kalikin LM: manuscript in preparation). However, these breakpoints are distributed over a surprisingly large distance, and thus more genes than IGF2 and H19 are probably involved.

What are the implications of imprinting for cancer genetic epidemiology? Our concepts of penetrance and genetic linkage must be modified. For example, most identical twins with BWS are discordant for the disorder. In addition, penetrance is determined by the parent from whom an imprinted gene is inherited. BWS kindreds typically show penetrance limited to the children of carrier mothers (regardless of whether the mothers themselves are affected). Fig. 1 illustrates a model pedigree in which a chromosome carries an imprinting mutation, i.e., it is defective in its ability to be switched from a paternal to a maternal epigenotype during gametogenesis. We would predict that some families with BWS would carry such an imprinting mutation. Note that the mutation is nonpenetrant when transmitted from a male, because the chromosome is supposed to be paternal, anyway, in that case. In particular, a girl whose mutation-bearing chromosome derives from her father is unaffected, yet any of her children bearing the mutation are affected. Complicating

the analysis is that there is no a priori way to know whether children of a man with a mutation-bearing chromosome carry the mutation or not. While carrier status in his daughter can be inferred from his daughter's children, carrier status in his sons cannot be deduced from his son's children.

Despite recent advances in molecular biology, pediatric oncologists are still unable to identify which patients with BWS are at the greatest risk of developing cancer. The incidence of BWS is approximately 1 in 10 000 live births. Thus, most tertiary-care pediatric centers will have limited experience in managing such patients. Consequently, clinicians have turned to nonspecific surveillance strategies to identify tumors in their earliest stages. Currently, there is no consensus for cancer screening in patients with BWS. However, many clinicians recommend an abdominal ultrasound every 3 months from birth until 7 years of age. This recommendation is based on the high risk of Wilms' tumor and hepatoblastoma in the first 10 years of life, approximately 10%, and the possibility of decreasing cancer-related morbidity and mortality if the tumor is identified at an earlier stage. Until we are able to identify the BWS genotype most likely to develop cancer, simulation models using a hypothetical cohort of patients with BWS can be applied to determine how screening for cancer should be done. Such cost-effective models are not ideal when attempting to decide the use of screening for cancer, since many of the key parameters in the models are estimates from nonempiric data. However, in situations where a cancer-screening trial is not a reasonable option, some quantitative methods must be applied to determine the use of screening.

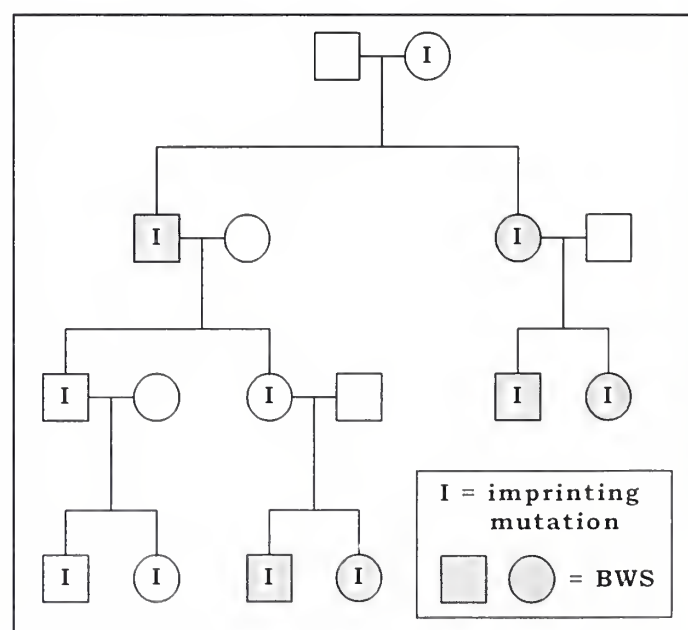


Fig. 1. A model pedigree illustrating a hypothesized imprinting mutation that prevents a switch from a paternal to a maternal epigenotype, for example in BWS. The mutation causes a maternally inherited chromosome to function like a paternally inherited chromosome. For clarity, children who do not inherit the mutation-bearing chromosome are not shown. (They are unaffected and do not transmit the disorder.) To be affected, one must inherit the mutation-bearing chromosome from one's mother. Note that there are likely to be multiple mechanisms of BWS, and that this figure is meant only to illustrate how defective imprintability of a chromosome could lead to a complex inheritance pattern.

Given the small number of patients with BWS, why is it important to study this cancer-predisposing syndrome rather than others? Historically, the study of rare cancer syndromes in pediatric patients has provided natural biological models for increasing our understanding of tumorigenesis, e.g., familial retinoblastoma and Li-Fraumeni syndrome. BWS is the most common pediatric cancer-predisposing syndrome and the phenotype is one of the most recognizable. Furthermore, since most patients with BWS receive cancer screening based on their phenotype, this syndrome offers an opportunity to evaluate the direct and indirect costs of screening for cancer in pediatrics, an area that will undoubtedly receive more attention as cancer-predisposing genes are discovered. Finally, BWS represents an opportunity to determine the epidemiologic effects of altered imprinting, e.g., to test models such as that shown in Fig. 1. One of the most interesting questions regarding BWS is whether imprinting disturbances that predispose to cancer may occur in patients not expressing or incompletely expressing the malformation phenotype. A corollary of this question is whether a larger fraction of the pediatric population at risk of malignancy might be identified by relatively inexpensive presymptomatic testing. This is one of the most important questions in strategies emerging for adult cancer surveillance. However, surveillance for pediatric tumors may also require epidemiologic and molecular correlates for genomic imprinting.

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Notes

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Molecular Markers in Cancer Diagnosis

David Sidransky*

Clonal genetic alterations are a hallmark of human cancer pathogenesis. These genetic alterations may include specific gene mutations that drive the cancer process or phenotypic changes such as microsatellite instability that may be caused by specific genetic events. Identification of clonal cell populations that share a specific genetic alteration is virtually synonymous with the detection of cancer. These clonal cells can be detected among a large population of normal cells from limited clinical samples by DNA amplification techniques. Because of their unprecedented sensitivity and specificity, these approaches offer new hope for the early diagnosis of human cancer. [Monogr Natl Cancer Inst 17:27-29, 1995]

Tumors arise through an accumulation of genetic changes in a variety of critical oncogenes (1). Mutations that lead to activation of proto-oncogenes and inactivation of tumor suppressor genes are an integral part of the initiation and progression of all human tumors (2,3). Point mutations are among the most common mechanisms for both activation and inactivation of these critical oncogenes. Although a variety of oncogene mutations are shared by entirely different kinds of cancer, some critical oncogene targets are more unique to each specific tumor type. For example, inactivation of p53 is found in almost all types of human cancer, including colon and bladder carcinomas (4). However, loss of chromosome 9p21 appears to inactivate a common tumor suppressor gene in many human cancers, including bladder carcinoma (5,6), yet this chromosomal region is rarely lost in colon carcinoma. Therefore, genetic events must be characterized for each type of neoplasia and must be arranged in a temporal order to develop a molecular progression model specific to each tumor type. Genetic changes that occur early in progression may take place in preneoplastic lesions that are still in an asymptomatic stage of clinical development. Thus, these genetic changes may provide rational markers for early cancer diagnosis.

Colorectal cancer is not the best characterized molecular model of cancer progression. This model was based on previous descriptions of histopathologic progression and careful correlation with specific genetic changes (7). On the basis of Knudson's original hypothesis on childhood tumors (8), tumor suppressor genes were predicted to reside in areas of chromosomal loss. For adult tumors, one copy of a critical suppressor gene would be inactivated in a somatic cell followed by mutation or loss of the second copy. Thus, inactivation of both suppressor alleles would lead to clonal outgrowth and neoplastic transformation. Loss of critical regions on chromosomes 5q, 17p, and 18q led to the discovery of important tumor suppressor genes in colorectal can-

cer. Importantly, the p53 gene (also known as TP53) on 17p and the DCC (deleted in colorectal carcinoma) gene on 18q appeared to be inactivated late in progression (7). Conversely, chromosome 5q was already lost in small, early lesions.

Further characterization of 5q loss led to the eventual identification of the APC (adenomatosis polyposis coli) gene within this region. Alterations of the APC gene were found to be responsible for the clinical cancer syndrome FAP (familial adenomatous polyposis) (9,10). Moreover, mutations of this gene were important in the initiation of many sporadic colorectal tumors (11). Recent studies have shown that mutations of critical mismatch repair genes, including MSH2, are responsible for hereditary nonpolyposis colon cancer (HNPCC) (12,13). Tumors from patients with HNPCC display widespread microsatellite instability throughout the genome. It is interesting that many sporadic tumors also contain occasional microsatellite alterations at certain repeat loci that are not necessarily associated with mismatch repair (14). Although there is little evidence that these microsatellite alterations specifically activate or inactivate critical oncogenes, they may still serve as excellent markers for identification of clonal cell populations (*see below*).

Proto-oncogenes also have a role in the initiation of colon cancers. Activation of the ras oncogene by point mutation is involved in approximately one half of sporadic adenomas and colon carcinomas. Moreover, like mutations of many proto-oncogenes, most ras gene mutations are clustered within a small region (codons 12 and 13). Because cancer cells are shed into the colonic lumen, they should be present in stool. We postulated that these cells would also carry the same genetic changes present in the primary tumors. Because of its small size and limited number of observed mutations, ras appeared to be an excellent target for molecular analysis of stool.

We developed a polymerase chain reaction (PCR)-based technique that allowed amplification from stool DNA followed by identification of specific gene mutations (15,16). This plaque hybridization assay, able to detect one cancer cell among 10^5 normal cells, employed cloning of PCR products followed by oligomer-specific hybridization. Furthermore, this technique allowed detection of clonal ras gene mutations and precise quantitation of the number of cancer cells present in a given stool sample. Initial studies successfully demonstrated identical ras mutations in stool samples from eight of nine patients with a ras gene mutation in their primary tumor. Importantly, among these

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patients were patients with small, resectable adenomas. In addition, patients without cancer and those without ras gene mutations in their primary tumor were consistently negative by this assay.

Others have used a similar approach to detect ras gene mutations in the stool of pancreatic cancer patients (17). Simpler assays involving allele-specific amplification (18) and enriched PCR (19) can also successfully detect rare ras gene mutations (Table 1) in bodily fluids. One of these studies (19) was aimed at asymptomatic high-risk patients with a personal or family history of colon cancer. Although these patients did not have visible tumors during the study, investigators demonstrated clonal ras mutations in a high percentage of these subjects. This approach demonstrates the potential use of molecular screening for early diagnosis, since gene mutations were detected before patients went on to develop cancer. In all of the studies to date utilizing molecular techniques, false-positives have not been reported. These DNA amplification techniques and other techniques like the ligase chain reaction (20) hold great promise for early detection of colorectal tumors in high-risk patients.

Because cytologic samples can also be obtained from nipple aspirates, breast cancer may also be amenable to a molecular screening approach (21). Mutations of p53 are ubiquitous in human cancers, including breast cancer, and can be detected in bodily fluids. Clonal p53 mutations have successfully been identified in urine from bladder cancer patients (15) and in the sputum of patients prior to the development of lung cancer (22). However, the timing of p53 mutations needs to be better defined in the progression of breast cancer. Losses of 17q are common in breast and ovarian cancers; thus, mutations of BRCA1 and other genes at this region are expected to be important events in the initiation of sporadic tumors as well (23). Furthermore, techniques aimed at identification of clonal microsatellite alterations as outlined below may also be of particular use in breast cancer. Identification of early genetic events in the progression of these tumors may yield other valuable molecular markers.

One major limitation of these molecular screening approaches has been the necessity to identify many different mutations in a variety of oncogenes. In an effort to search for more feasible markers, we turned our attention to microsatellite alterations (24). We have recently determined that certain "hypermutable" microsatellite loci may be more susceptible to expansions or deletions. These alterations often include the larger (tri- and tetra- nucleotide) repeats spread across the entire genome. Current evidence suggests that these alterations probably arise in a

transformed cell as a replication error during cell division. These alterations are then propagated to daughter cells (harboring the same genetic advantage) during clonal expansion. The detection of a novel expansion or deletion appears restricted to monoclonal neoplastic tissue. If the replication error occurs in a cell that does not undergo clonal expansion, it would not be detected among the large excess of DNA from surrounding cells. A single PCR amplification of DNA from clinical samples allows detection of these clonal genetic alterations by simple microsatellite analysis.

We have demonstrated the presence of these clonal changes in urine samples from patients with bladder cancer and in sputum from patients with lung cancer (24). This analysis can detect about one cancer cell among 500 normal cells and could be a valuable adjunct to cytologic diagnosis. Colorectal cancers may be particularly amenable to this detection strategy because of the high frequency of microsatellite alterations observed in these tumors. Prospective evaluation of samples to detect clonal cell populations should identify patients at high risk of neoplastic progression and/or those who have already developed cancer. This test may offer a relatively low cost molecular approach for cancer detection.

Characterizing the molecular progression of each tumor type is critical in order to target early events for diagnostic molecular studies. Colorectal cancer has been at the forefront, with a variety of critical genetic steps already well placed along the progression pathway. However, important strides are being made in many other solid tumors. Loss of chromosome 9p appears to target a critical tumor suppressor gene potentially involved in the initiation of many neoplasms. Identification of the putative tumor suppressor gene at this locus may provide another common molecular marker applicable to a variety of neoplasms. Continued surveys of microsatellites should yield many more valuable hypermutable loci for use as clonal markers. Furthermore, continuing improvements of PCR-based technologies will greatly simplify the ability to detect all of these clonal genetic alterations in clinical samples.

To validate these new technologies, paired tumor and bodily fluid samples need to be collected and stored (25). One recent case study of a prominent individual (26) demonstrated the potential power of this approach. Available studies already suggest that the identification of these gene mutations prior to clinical diagnosis may allow detection of tumors when they are still amenable to surgical resection and possible cure.

Table 1. Molecular screening in primary cancers: highlights of recent PCR-based molecular screening approaches for primary human tumors*

Study—investigators, ref. No., year	Site of neoplasm	PCR technique	Bodily fluid	No. of cancer patients	No. of control patients
Sidransky et al. (15), 1991	Bladder	Plaque hybridization	Urine	3	3
Sidransky et al. (16), 1992	Colon	Plaque hybridization	Stool	9	6
Tada et al. (18), 1993	Pancreas	Allele-specific amplification	Pancreatic juice, blood	7	5
Caldas et al. (17), 1994	Pancreas/bile duct	Plaque hybridization	Stool	14	3
Tobi et al. (19), 1994	Colon	Enriched PCR	Colonic effluent	20 [†]	19
Mao et al. (22), 1994	Lung	Plaque hybridization	Sputum	10	5

*Details of each molecular technique are described in the respective studies.

[†]High-risk patients without visual evidence of a neoplasm.

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Surgical Prophylaxis of Familial Colon Cancer: Prevention of Death From Familial Colorectal Cancer

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Patients at risk for inherited colorectal cancer constitute a heterogeneous population. A total colectomy is minimal treatment for those patients with invasive cancer or those with established risk factors. For others at risk, predictive genetic markers, correlated with clinical and pathologic determinants, will establish the basis for policies of surveillance and preventive surgery. [Monogr Natl Cancer Inst 17:31-32, 1995]

Although primary management of patients with curable, familial colorectal cancer is operative, the larger challenges are as follows: case finding, application of early appropriate treatment to those with or without colorectal cancer, and recognition of need for systemic surveillance of these patients. The call-up case does better than the index patient. Prevention of death from familial colorectal cancer embraces a far wider umbrella of health care skills than operative techniques.

Some patients with inherited colorectal cancer have clearly defined risk factors on the basis of clinical and pathologic correlations. Other patients, poorly understood, await clarification from progress in molecular biology. The need for and extent of surgery depends on prediction of risk.

When risk merits surgery, treatment options are few. The patient who has familial adenomatous polyposis (FAP), with or without invasive cancer, needs either a total colectomy and ileorectal anastomosis or a total proctocolectomy with reconstruction by an ileoanal anastomosis and pelvic reservoir (1).

In the setting of hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndromes, a patient with curable, invasive colorectal cancer, often in the right colon, who may or may not have additional colorectal adenomas, also needs a total colectomy and an ileorectal or ileosigmoid anastomosis. For almost 40 years, removal of the colon, even in the setting of sporadic colon cancer with a few scattered adenomas, has been accepted management in appropriate circumstances (2,3). When colon surgery is planned for a woman with the Lynch 2 syndrome, bilateral oophorectomy and hysterectomy should also be considered, particularly if the woman is postmenopausal.

The difficult questions relate to prophylactic colectomy. Removal of an apparently healthy organ without neoplasia seems draconian and, in the words of Lewis Thomas, a "halfway technology." A pre-emptive strike may leave innocent casualties. Indeed, the aim of this conference is progress in detection

of genetic risk and conversion of molecular insights to rational policies for surveillance and treatment.

In the meantime, the clinician must assess risk by reliance on historical and descriptive factors. Young age at onset of colorectal cancer is suggestive, but about four of five such young persons appear to be the extreme tail of a distribution curve of a common sporadic cancer (4,5). Presence of other phenotypic expressions, such as desmoid disease, osteomas in the polyposis patient, or breast, ovarian, or endometrial cancer, may indicate inherited risk of colorectal cancer. In these circumstances, surveillance is surely warranted.

The most useful clues arise from family history. About 15% of patients with colorectal cancer have a family history of colorectal cancer in one or more first-degree relatives. Several subpopulations reside within this heterogeneous group. Some patients with a family history of colorectal cancer represent a chance admixture of a frequent cancer or, possibly, common environmental promoting events. Familial associations of colorectal cancer were determined by Lovett (6) among 209 patients with colorectal cancer without polyposis, and empiric risk was calculated by Murday (7). Presence of colorectal cancer in three first-degree relatives was defined as autosomal dominant and identified with the Lynch syndromes. Does this level of risk merit preventive colectomy in a sibling without cancer? In the added presence of defective HNPCC genes, the answer seems affirmative.

About 1% or fewer such patients have FAP, the result of a germline mutation of the APC gene at locus 5q21. The patient with FAP can now be identified by a protein- and allele-specific expression assay (8). The patient with FAP is readily recognized by numerous colorectal adenomas first appearing at adolescence or earlier. Early phenotypic expression may include bilateral retinal pigmentation. Because risk of invasive colorectal cancer starts at about age 20, surgery is usually deferred to mid-adolescence or late adolescence when the patient can participate in the treatment decisions.

The term "Gardner's syndrome" has been applied by some to embrace extracolonic expressions associated with FAP. Molecular studies have shown a similar allelic defect in both (9). All patients with FAP are at risk for life-threatening extracolonic

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expressions, particularly periampullary cancer and desmoid disease. The patient with polyposis needs life-long systemic surveillance. There may be a reciprocal relationship in the intensity of epithelial or mesenchymal expressions at that gene locus (10).

Some patients have HNPCC, or Lynch syndromes, associated with cancer at other sites, particularly ovary and endometrium, and with defined, heterozygous, germline, mismatch-repair genes at loci 2p16 (11) and 3p21-23 (12). Population-based data are not yet available; however, in the experience of hospital-based registries, patients with the Lynch 2 syndrome appear less often than those with FAP. Molecular analysis of inherited colorectal cancer syndromes is far from complete.

Other rare, inherited polyposis syndromes are defined by the histology of the colorectal polyp. These include the Peutz-Jeghers syndrome with hamartomatous polyps and juvenile polyposis with retention polyps. Both syndromes carry a small increased risk of colorectal cancer.

What emerges from scrutiny of inherited colorectal cancer risk are several, possibly intersecting, subgroups: some characterized by a distinctive histology, some labeled by a germline molecular marker, and some not defined at all. There appears to be substantial ascertainment bias in descriptive classification of these syndromes: we are on the threshold of clarification from molecular genetics. New pathways will emerge from genotype-phenotype correlations, and existing syndromes will be reclassified. Valid markers, particularly those identified during induction and promotion, not progression, will provide the basis for feasible screening policies and, with clinical and pathologic correlations, for decisions regarding treatment.

In the absence of colorectal cancer and in the absence of predictive clinical or genetic markers, a preventive colectomy cannot be recommended, and one must turn to surveillance. The American Cancer Society recommends that persons with a family history of colorectal cancer in one or more first-degree relatives with an onset at age 55 or younger begin an annual fecal occult blood test and a colonoscopy or double-contrast barium enema examination every 5 years, starting at age 35-40 years (13). Colorectal adenomas should be removed by endoscopy. Recommendations from Fitzgibbons et al. (14) are more aggressive: biannual fecal occult blood testing should begin at age 20 and yearly colonoscopy at age 25, or 5 years before onset of the earliest colon cancer in the family.

In summary, the minimal treatment of a patient with curable, invasive colorectal cancer in the setting of an inherited colorectal cancer syndrome is total colectomy. On identification of the

proband, prevention (or prophylaxis) requires that health care resources, embracing family practitioners, internists, gastroenterologists, oncologists, geneticists, registrars, social workers, and surgeons, reach out to contact members at risk within the proband's pedigree and initiate proper surveillance. Policies for surveillance and for preventive operative management of persons without invasive cancer will depend on evidence derived from predictive molecular markers. At the same time, these molecular markers can provide the end points for primary prevention, particularly nutritional and pharmacologic efforts to inhibit human carcinogenesis.

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Note

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Prophylactic Oophorectomy in Inherited Breast/Ovarian Cancer Families

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Prophylactic oophorectomy is chosen by some women at high risk of ovarian cancer due to inherited predisposition. Unfortunately, this surgery is not 100% effective in preventing intra-abdominal carcinomatosis that histologically resembles ovarian cancer. To determine the incidence of post-oophorectomy carcinomatosis and to quantify the effectiveness of preventive surgery, a multicenter study is ongoing between the National Cancer Institute (NCI), Creighton University, and the United Kingdom. The prospective incidence of malignancy, especially of tissues derived from coelomic epithelium (primarily ovary, fallopian tube, and peritoneum), was compared between women of similar genetic risk who have or have not undergone oophorectomy. Analysis of 12 NCI families has been completed. Prospective observation ran from the date of family ascertainment until the date of cancer incidence, death, or December 31, 1992. Approximately 1600 person-years of observation occurred among 346 first-degree relatives of a breast or ovarian cancer case patient for women who had not undergone oophorectomy. Eight ovarian cancers occurred, compared with two carcinomatosis cases during 460 person-years of observation among 44 oophorectomized women. Compared with Connecticut Tumor Registry data adjusted for age, race, and birth cohort, there was an approximately 24-fold excess of ovarian cancer among non-oophorectomized women and a 13-fold excess of "ovarian" cancer among oophorectomized women, though this difference was not statistically significant. The confidence intervals around these numbers were large, and a collaborative analysis will be required to determine whether this apparent protective effect is real. [Monogr Natl Cancer Inst 17:33-35, 1995]

Genetic predisposition to ovarian cancer may be due to several syndromes, including inherited ovarian cancer, inherited breast/ovarian cancer, and Lynch Syndrome II. Most inherited breast/ovarian cancer families appear to be linked to the BRCA1 gene on chromosome 17 (1). The penetrance for breast or ovarian cancer in BRCA1-linked families appears to be greater than 80% (1). In an analysis of a subset of 33 clearly linked breast/ovarian pedigrees from the international consortium, 44% of individuals with breast cancer also developed ovarian cancer, and by the lod (i.e., logarithm of odds) score maximization method, the estimated penetrance for ovarian cancer in these families was about 67% (2). Clearly, there is genetic hetero-

geneity with regard to ovarian cancer for BRCA1 because some linked families have no cases of ovarian cancer, while others have more cases of ovarian cancer than of breast cancer.

Because of the high risk of ovarian cancer with inherited syndromes, screening and preventive methods are important. Screening, although recommended for high-risk women with inherited predisposition, is unproven and suffers from lack of both sensitivity (especially for serum markers) and specificity (especially for ultrasound). Preventive oophorectomy is an option chosen by some women with inherited predisposition. The decision to have an oophorectomy after childbearing is complete is often a difficult one. In addition, there are many difficult clinical issues, including the timing of and type of surgery, concurrent hysterectomy, and hormone replacement therapy. And, unfortunately, the surgery is not completely effective in preventing intra-abdominal carcinomatosis that histologically resembles ovarian cancer.

In 1982, among 16 potentially inherited ovarian and breast/ovarian cancer families studied at the National Cancer Institute (NCI), preventive oophorectomy had been performed on 28 women (3). Three cases (11%) of carcinomatosis occurred 1-11 years after oophorectomy. There was no other primary site identified, and available slides and recut paraffin blocks from the oophorectomies were free of malignancy. This observation caused much concern and pointed to the need to inform women considering prophylactic oophorectomy that the surgery may not completely eliminate the risk of intra-abdominal carcinomatosis. To determine more accurately the incidence of post-oophorectomy carcinomatosis and to quantify the effectiveness of preventive oophorectomy, a multicenter study is planned between the Genetic Epidemiology Branch of NCI, the Department of Preventive Medicine of Creighton University, and the Institute of Cancer Research Section of Epidemiology and Department of Pathology of Cambridge University in the United Kingdom. Prepared for a presentation at a workshop on hereditary breast, ovarian, and colon cancers, preliminary analysis from one center is presented here.

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Methods

A pilot study was conducted using data from families that were collected at the Genetic Epidemiology Branch of the NCI. Eligible families included those with at least three documented cases of ovarian cancer or those with at least two documented cases of ovarian cancer and at least one documented case of breast cancer occurring before age 50. Families fitting the criteria for Lynch Syndrome II were excluded. Sixteen families meeting these criteria were ascertained between 1969 and 1980, but four families were lost to follow-up and were not included in this study. The incidence of malignancy from tissues derived from the coelomic epithelium (primarily ovary, fallopian tube, and peritoneum) among members of these families was calculated from the date of family ascertainment. All cancers that occurred before this date were excluded. All women were characterized as to their risk of being a gene carrier (at birth) by determining the closest relative affected with breast and/or ovarian cancer. Although the estimated risk of being a gene carrier decreases the longer a woman survives cancer free, genetic risk at birth was used because age is controlled for in the analysis. Genetic risk based on linkage analysis could not be estimated for most families because most affected individuals were dead and no DNA was available.

Cancer incidence was compared between women of similar genetic risk who had or had not undergone oophorectomy. The O/E program (IMS, Inc., Silver Spring, Md.) was used to calculate person-years of observation and to compare observed-to-expected incidence rates.

Results

Approximately 1600 person-years of observation occurred among first-degree relatives of a breast or ovarian cancer case patient among non-oophorectomized women from the 12 families. Eight ovarian cancers occurred prospectively, compared with two prospective post-oophorectomy cases, during 460 person-years of observation among oophorectomized women (one of the known post-oophorectomy cases in these families oc-

curred immediately before family ascertainment and was therefore excluded) (Table 1). Compared with Connecticut Tumor Registry data adjusted for age, race, and birth cohort, there was an approximately 24-fold excess of ovarian cancer among non-oophorectomized women and a 13-fold excess of "ovarian" cancer among oophorectomized women. The confidence intervals around these numbers were large, and the collaborative analysis will be required to determine whether this apparent protective effect is real. It is interesting that there appeared to be a protective effect of similar magnitude for breast cancer among women who had undergone oophorectomy (Table 2).

Discussion

Prophylactic oophorectomy is chosen by some women because of their high risk of ovarian cancer due to inherited predisposition. When the BRCA1 gene is cloned, and especially if some mutations are correlated with ovarian cancer incidence, this option may be chosen by even more women known to carry such a mutation. It is therefore vital to determine precisely the effectiveness of this procedure, given the disturbing possibility of post-oophorectomy carcinomatosis.

Three explanations have been proposed for the occurrence of post-oophorectomy carcinomatosis that is histologically similar to ovarian cancer: 1) There may have been an occult ovarian malignancy present at the time of oophorectomy that had already metastasized but that was not clinically detectable; 2) the source of the malignancy may be ectopic ovarian tissue; and 3) the source of the malignancy may be the peritoneum, which is derived from coelomic epithelium, the same embryologic origin as the surface epithelium of the ovary, the histologic type of more than 90% of all ovarian cancers. The entire abdominal peritoneum may be at risk of malignant transformation. While removing the ovaries may remove the most likely source, it may not remove all at-risk cells.

Since the initial report in 1982 (3), no additional cases are known to have occurred in the NCI families. However, several other cases have been reported in the literature. One occult case was reported (4), and several other individual case reports have

Table 1. Preliminary analysis of "ovarian" cancer incidence after oophorectomy in 12 NCI families

Group	Oophorectomy	Person-years	No. of "ovarian" cancers	Observed/expected	95% confidence interval
First-degree relative	No	1665	8	24	10-47
	Yes	460	2	13	1-47
Second-degree relative	No	2123	1	3.5	0-19
	Yes	106	0	—	0-79

Table 2. Preliminary analysis of breast cancer incidence after oophorectomy in 12 NCI families

Group	Oophorectomy	Person-years	No. of breast cancers	Observed/expected	95% confidence interval
First-degree relative	No	1587	14	7	4-12
	Yes	484	3	2.7	0.5-8
Second-degree relative	No	2131	3	1.7	0.3-5
	Yes	106	0	—	0-17

been published (5,6). The largest series was from the Gilda Radner Familial Ovarian Cancer Registry, where six documented cases (2%) occurred among 324 women from nearly 1000 families registered (7). The cases occurred from 1 to 27 years after oophorectomy.

The accurate determination of this entity is difficult. While it may most likely occur in families with an inherited predisposition to ovarian cancer, such families are usually referred and may be biased toward those in which a post-oophorectomy case has occurred. However, if all cancers that occurred before family ascertainment are excluded, prospective incidence in these families would be a less biased estimate of the true incidence of this condition. But since the incidence of ovarian and peritoneal cancers is relatively low even in these high-risk pedigrees, a collaborative effort is necessary to obtain enough power to estimate its incidence with a reasonable confidence interval. The three centers participating in this collaborative effort have been studying inherited ovarian and breast/ovarian cancer families for several decades. This situation allows the observation of a sufficient number of person-years, after ascertainment, to address these issues.

The risk of ovarian cancer in inherited ovarian cancer families studied to date, particularly those linked to BRCA1, is very high—in the range of 45% to as high as 67% or more. There is also no proven means of effectively screening for this lethal

cancer, and preventive surgery should be a consideration. However, there is a finite risk of post-oophorectomy carcinomatosis. While this preliminary analysis suggests a statistically nonsignificant protective effect of the surgery for ovarian cancer, the risk in oophorectomized women was still much higher than the risk of ovarian cancer in the general population. Further collaborative study will be required to determine more precisely this finite risk.

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Bilateral Prophylactic Mastectomy: Issues and Concerns

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At present, the care of women at increased risk of developing breast cancer poses a clinical dilemma and remains an area of controversy. A number of investigators have addressed the pros and cons of prophylactic mastectomy versus close follow-up, utilizing annual mammography, semiannual or even more frequent physical examinations of the breast, and proficient monthly breast self-examinations. Recent efforts to isolate a gene (BRCA1) on chromosome 17q12-21 raise additional concerns about the management of women testing positive for BRCA1 mutations. These women are estimated to have an 85% lifetime risk of developing breast cancer. Testing for BRCA1 mutation carriers may soon be available for population screening. This article describes preliminary studies investigating health care provider and patient perceptions of bilateral prophylactic mastectomy. In addition, a number of research questions remain regarding the efficacy and utilization of bilateral prophylactic mastectomy as a treatment option for women at increased risk of developing breast cancer. These women include those testing positive for BRCA1 mutations. In addition, women with a strong family history opting against testing for BRCA1 mutations may express interest in surgery. [Monogr Natl Cancer Inst 17:37-42, 1995]

One of the most controversial procedures to prevent breast cancer includes bilateral prophylactic mastectomy, i.e., the bilateral removal of noncancerous breast tissue to prevent cancer. Prophylactic mastectomies may reduce breast cancer risk in women without breast cancer. The identification of women at sufficiently high risk to warrant consideration for such a procedure is a critical and often discussed aspect of this issue in the professional literature and lay press (1-5).

The indications for recommending prophylactic mastectomy among high-risk women are controversial. Historically, investigators have focused on women with 1) two or more first-degree relatives with breast cancer, 2) several breast biopsies demonstrating proliferative breast disease, 3) repeated breast biopsies with resulting breast deformity, 4) therapy-resistant gross cystic disease with intolerable pain, or 5) severe cancerophobia as possible candidates for prophylactic mastectomy (1-3).

The impending identification of BRCA1 (6), a major gene foci involved in inherited breast cancer, and its potential use in screening tests may have a significant impact on the interest in prophylactic mastectomy among both health care providers and women testing positive for BRCA1. Efforts are currently under

way to isolate this gene on chromosome 17q12-21 (7). Patients with mutations on this gene, predisposing women to breast and ovarian cancers, have an 85% lifetime risk of developing breast cancer (8). It is estimated that one in 200-400 U.S. women may be carriers of BRCA1 mutations. While it is not currently possible to perform DNA testing to confirm the presence of the gene, it is expected that this test may be available in the next several years. Of significance is the fact that women testing negative for BRCA1 may be at high risk for breast cancer development through other mechanisms, including germline mutations in genes other than BRCA1.

There is a host of unresolved issues related to the use of bilateral prophylactic mastectomy as a management option to prevent breast cancer in women at increased risk of developing this disease. The remainder of this article will address health care provider perceptions of bilateral prophylactic mastectomy and some information on patients' perception of this surgery, including possible predictors of bilateral prophylactic mastectomy decision making. Finally, the article will conclude with unresolved research questions related to this surgery.

Health Care Provider Perceptions

Little information is available on the attitudes of health care providers on the practice of prophylactic mastectomy. Only case reports and case series have been described (1,9,10). In a study assessing clinical decision making, Belanger et al. (11) provided oncologists and oncology nurses with a clinical vignette that described a patient at high risk for developing breast cancer. Questionnaires were returned from 250 oncologists and nurses (54% response rate) selected from the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology, the Surgical Society of Oncology, and the American Nursing Oncology Society. These practitioners were asked to describe how they would manage this patient at high risk. In addition, female physicians and oncology nurses were asked to consider themselves as the patient in the scenario and to select a treatment option. The scenario for the patient at high risk was as follows (11): "The patient is 26 years old with 2 small children. Her mother died of breast cancer at age 52, and her oldest sister developed bilateral breast cancer and died at

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age 39 of metastatic disease. The last routine mammogram that you ordered showed signs of bilateral dysplasia but no evidence of malignant lesions. The breast examination showed multiple small lumps less than 1 cm but none suggested a malignancy. How would you treat this woman?"

The woman in the above scenario would have an approximately 35%-40% risk during the next 30 years (12). Approximately one third of all physicians surveyed selected bilateral prophylactic mastectomy, while one third selected careful follow-up and one third indicated that they would present both options to the patient and let her decide. Medical oncologists were slightly more likely to recommend bilateral prophylactic mastectomy, as were physicians younger than age 40.

When female providers were asked what choice they would make if they were the patient, 50% of radiation oncologists and 86% of medical oncologists selected bilateral prophylactic mastectomy. Forty-four percent of oncology nurses selected bilateral prophylactic mastectomy for their treatment, given the risk status of the woman in the scenario above.

Houn et al. (13) conducted a survey of Maryland general surgeons, plastic surgeons, and gynecologic surgeons to determine the number of bilateral prophylactic mastectomies recommended and performed in an average year and to determine what factors might influence surgeons on the management of high-risk women. All general surgeons, plastic surgeons, and gynecologic surgeons who had completed their residency and/or subspecialty training and were licensed to practice in the state of Maryland in 1992 were included in this survey. Of the 1480 surgeons identified, 37% were general surgeons, 5% were plastic surgeons, and 57% were gynecologic surgeons. Fifty-one percent of the questionnaires were returned and eligible for analysis. A significant number of surgeons responding indicated that bilateral prophylactic mastectomy has a role in the management of women at high risk of developing breast cancer (Table 1).

The surgeons were presented with a vignette in addition to the questionnaire and were asked to make a decision regarding management of a woman at increased risk of developing breast cancer. The vignette read as follows (13): "A 35 year old woman presents with a family history of breast cancer occurring in 1 of 3 sisters at the age of 38 and her mother at age 50. Her menarche was at age 12; her first child was at age 27. She is very worried about breast cancer and asks for your advice. What would you recommend?"

The woman in this scenario has an approximately 25% risk of developing breast cancer during the next 30 years, according to the model of Gail et al. (14). Six percent of the total respondents selected bilateral prophylactic mastectomy as their management

option of choice. Thus, the overwhelming number of surgeons across specialty areas selected surveillance, including mammography, clinical breast examination, and breast self-examination as their treatment option.

Survey respondents were asked about the breast cancer risk needed to prompt a recommendation of prophylactic mastectomy. The surgeons responding required a 40%-55% lifetime risk of developing breast cancer before they recommended prophylactic mastectomy as a management option. Eighteen percent of the gynecologic surgeons, 39% of the general surgeons, and 81% of the plastic surgeons reported ever recommending prophylactic mastectomy. Finally, 53 plastic surgeons reported completing 56 bilateral prophylactic mastectomies in 1991, while 219 general surgeons reported performing 45 bilateral prophylactic mastectomies in the same calendar year.

It appears from these studies that bilateral prophylactic mastectomy is viewed as a possible management option for women at increased risk of developing breast cancer, and the surgery is being recommended and performed. On the basis of the data obtained by Houn et al. (13), a significant minority to a majority of surgeons endorse the statement that prophylactic mastectomy has a role in the management of women at increased risk of developing breast cancer. The distribution of threshold risk that would prompt recommendation for surgery suggests that there is not yet a clear consensus with regard to the degree of risk needed to recommend or perform surgery. In addition, the threshold risk selected across specialties may indicate consideration of surgery by providers in these specialties for women with positive results from genetic screening for breast cancer. Finally, plastic surgeons may recommend and perform proportionately more prophylactic mastectomies than the two other specialty groups. This finding is particularly tentative, given the small number of plastic surgeons responding to the survey. It is possible that patients referred to the plastic surgeons have a somewhat higher risk or may have already consulted general surgeons and gynecologic surgeons and were referred to plastic surgeons. Alternatively, plastic surgeons may be able to address the issue of reconstruction, which may make prophylactic mastectomy more acceptable to some women and lead to more procedures being recommended and performed by surgeons in this specialty.

Patient Perceptions

At present, little is known about the satisfaction of women undergoing bilateral prophylactic mastectomy and about the decision-making process involved, i.e., the predictors involved

Table 1. Agreement or disagreement that bilateral prophylactic mastectomy has a role in the management of women at high risk of developing breast cancer*

	General surgeon (n = 215)		Plastic surgeon (n = 52)		Gynecologic surgeon (n = 433)		Total (n = 700)	
	%	No.	%	No.	%	No.	%	No.
Agree	47.0	101	84.6	44	38.3	166	44.4	311
Disagree	30.2	65	5.8	3	29.1	126	27.7	194
Neither agree nor disagree	22.8	49	9.6	5	32.6	141	27.9	195

*Reproduced from (13).

in the decision to have surgery versus intensive surveillance. A recent report by Stefanek et al.¹ examined satisfaction with the procedure and factors related to making the decision about prophylactic mastectomy surgery. Participants in the study (n = 136) were women with at least one first-degree relative diagnosed with breast cancer seen at a clinical service for women at increased risk. Three groups of women were reported on for this study. Fourteen women seen at this service expressed initial interest in this surgery and completed bilateral prophylactic mastectomy subsequent to their visit to this service. Women in a second group (n = 64) expressed interest in this surgery prior to the high-risk service visit, but they decided against the prophylactic procedure. Finally, a third group (n = 58) did not express interest in the option of bilateral prophylactic mastectomy.

All women who had a prophylactic mastectomy reported satisfaction with the surgery a minimum of 6 months after completion of the procedure. Dimensions of the survey included satisfaction with the time needed to recover from the surgery (physically and emotionally), the degree of discomfort after surgery, satisfaction with their support system, and overall satisfaction with the decision to have the prophylactic mastectomy. All of the women (n = 14) undergoing surgery reported satisfaction, both with the decision to have the prophylactic mastectomy and on the dimensions noted above. Findings on biopsies at the time of prophylactic mastectomy indicated epithelial hyperplasia (n = 3), lobular carcinoma in situ (n = 1), and infiltrating tubular carcinoma (n = 1).

The results of breast reconstruction were somewhat more mixed. While three women opted against breast reconstruction, three women reported dissatisfaction with the procedure, including two who required implant removal because of tissue rejection and subsequent infection.

The following variables were examined to determine differences among women opting for surgery, women interested in but opting against surgery, and women not interested in bilateral prophylactic mastectomy:

- Age
- Number of affected first-degree relatives
- Number of biopsies
- Subjective risk
- Objective risk

- Mammography adherence
- Clinical breast examination adherence
- Breast self-examination frequency
- Confidence in breast self-examination
- Breast cancer worry
- Depression
- Belief in prevention
- Belief in early detection
- Breast cancer event in last year
 - Personal history of biopsy
 - Family history of biopsy
 - Diagnosis of family member
 - Recurrence in family member
 - Death of family member as a result of breast cancer

Table 2 notes statistically significant differences between groups in regard to these variables. While a history of biopsies and subjective risk estimates differentiated the two groups having an interest in prophylactic mastectomy versus noninterested women, these variables did not differentiate those women opting for surgery from those reporting an interest in the surgery but selecting close follow-up. However, worry about breast cancer development was significantly different across all three groups. This finding of higher levels of self-reported anxiety among women opting for surgery is consistent with an earlier pilot investigation (15).

On the basis of this investigation, a significant minority to a majority of women initiating a visit to a service for women at increased risk of developing breast cancer may express an interest in the management option of prophylactic mastectomy. In addition, satisfaction with prophylactic surgery may be very acceptable among a sample of women reporting strong family and friend support and following formal risk counseling. Satisfaction with breast reconstruction, while generally favorable, may be less consistent than with the surgery proper. Finally, subjective risk estimates, biopsy histories, and worry related to breast cancer development should continue to be investigated as variables influencing decisions for close breast cancer-screening follow-up versus prophylactic mastectomy.

Obviously, the findings related to both provider and patient perceptions are quite tentative, given the relative dearth of information in this area and given the small sample sizes of these investigations. Further research examining provider perceptions and patient perceptions of this surgery is much needed.

Table 2. Prophylactic mastectomy (PM) decision making: group differences*

	PM group 1 (n = 58)	PM group 2 (n = 64)	PM group 3 (n = 14)	Significance
History of biopsies: No. (%)	14 (24)	31 (48)	7 (50)	Group 3, 2>1†
Subjective risk: mean (SD)				
10 y	36.8% (26.8)	48.8% (23.3)	59.2% (25.6)	Group 3, 2>1†
30 y	51.8% (27.0)	57.4% (23.8)	70.4% (22.1)	Group 3>1†
Breast self-examination frequency: No. (%)				
More than monthly	9 (17)	18 (30)	6 (46)	Group 3>1†
Monthly	28 (53)	4 (41)	7 (54)	
Less than monthly	16 (30)	17 (29)	0 (0)	
Worry (range, 1-7): mean (SD)	2.6 (1.3)	3.4 (1.6)	5.2 (1.8)	Group 3>2>1‡

*Group 1 = not interested in surgery; group 2 = interest only—no surgery; group 3 = surgery group.

†P<.05.

‡P<.001.

Research Questions

How Preventive Is Prophylactic Mastectomy?

Surprisingly little is known about the true preventive value of bilateral prophylactic mastectomy. A number of animal studies have examined the validity of the notion that a surgical reduction of the tissue at risk results in a corresponding reduction in risk of breast cancer. Kliner et al. (16) administered a known mammary carcinogen (7,12-dimethylbenz[*a*]anthracene) and then performed unilateral mastectomies on 60 Sprague-Dawley rats and sham incisions on 60 Sprague-Dawley control rats; they followed these rats continuously to monitor the incidence of breast tumors. While breast cancer development was decreased in the animals receiving mastectomies 15 weeks after surgery, after 77 weeks there was no difference in the number of animals with neoplastic tumors. In other words, the incidence of carcinogen-induced mammary neoplasms in these rats progressed with time. While surgical reduction of breast tissues was followed by early reductions in neoplasia, the difference was not maintained. This finding is not inconsistent with other investigations (17,18) that found the overall risk of breast tumors not significantly reduced by prophylactic mastectomy. Indeed, Wong et al. (18) found that residual breast tissue after prophylactic mastectomy was at increased risk for the development of tumors. However, for a number of reasons, we must be cautious in fully extrapolating these results to the human situation. The influence of a carcinogen on breast tissue in these animal models may be substantially different from the genetic influence on breast tissue in women with a strong family history of breast cancer. All rodent breast tumors are generally characteristically multifocal, and tumors often grow to a large size without metastasizing. Finally, human breast cancer is generally not viewed as a cancer with a chemical carcinogen as a significant risk factor (19).

Temple et al. (20) reviewed 10 mastectomy specimens to identify the extent of surgery necessary to completely remove all breast tissue in patients having prophylactic mastectomies. The surgical operation included a bilateral total mastectomy in each patient. Results indicated breast tissues in areas either not suspected or not realized previous to this study. The authors noted that, on the basis of this study, a total extirpation of all glandular breast tissue would include even more extensive surgery than that routinely done for total mastectomy for cancer. They recommended that if this total glandular extirpation is intended, then mastectomy must be extended to a layer of pectoralis major fascia and into the lower level axilla. The lower flaps must be made very thin. However, the authors also noted that the prophylactic value of this surgery still remains to be shown.

Other investigators (21) have expressed concerns regarding involvement of the nipple areola in breast cancer even in tumors distant from the nipple, whereas others (9,22,23) have noted a recurrence of breast cancer after prophylactic subcutaneous mastectomies. The surveys with the largest sample of patients include those of Pennisi and Capozzi (9) and Woods (24). Their findings indicate an incidence of subsequent carcinoma following mastectomy of 0.1%-0.2% among more than 2000 surgeries. However, these reports generally involved short follow-up inter-

vals and were often done for a variety of reasons, including fibrocystic disease, in addition to proliferative diseases of the breast and family history. Furthermore, some patients with *in situ* malignancy were treated with total or radical mastectomy instead of subcutaneous surgery. Thus, these numbers may underestimate the risk of cancer subsequent to prophylactic surgery.

Surgery more extensive than that involved in subcutaneous surgical procedures may not be truly preventive. Holleb et al. (25) reported two cases of breast carcinoma 10-15 years after simple mastectomies for benign conditions had been performed.

Thus, it appears that prophylactic mastectomy, whether subcutaneous or total, may reduce, but likely not eliminate, the risk of breast cancer. Patients should obviously be aware of this fact before a prophylactic mastectomy is performed. The prospective patient and physician should be prepared to continue regular monthly self-examination and routine examinations by health care providers. Obviously, further collection of data is needed to substantiate whether or not the incidence of breast cancer following bilateral prophylactic mastectomy is decreased or eliminated. Until this information is available, we cannot consider bilateral prophylactic mastectomy to be truly "prophylactic."

What Criteria Should Be Used to Initiate the Discussion of Prophylactic Mastectomy?

In the study by Houn et al. (13), the threshold risk at which surgeons would recommend prophylactic surgery was quite variable (40%-55%). Differences were noted across specialties, with plastic surgeons reporting a lower threshold than gynecologic surgeons. Many discussions in the literature regarding the needed risk for consideration for preventive surgery hover around 25% (1,2). The "threshold" risk does not appear to be consistent either within or across medical disciplines involved in decision making regarding prophylactic mastectomy. Important to note is that this threshold risk is consistent with the risk among women testing positive for BRCA1 mutations.

What Are Provider Opinions Regarding the Role of Preventive Surgery for Women Testing Positive on Genetic Testing or Women Opting Against Testing?

Testing for BRCA1 gene mutations may be available in the near future. We have little information on provider opinions regarding bilateral prophylactic mastectomy in general. The studies by Houn et al. (13) and Belanger et al. (11) are the only two addressing this question. The scenarios presented to the providers in these studies do not address the issue of genetic testing. It is unclear how the testing for genetic mutations will alter provider opinion on surgery versus close follow-up without surgery. It is certainly possible that some providers may utilize testing as a criterion upon which to base surgical decisions.

What Are the Perceptions of Women at Increased Risk of Developing Breast Cancer Regarding Bilateral Prophylactic Mastectomy Versus Close Follow-up?

Little information is currently available addressing this question. The study by Stefanek et al.¹ investigated this issue among

a sample of women attending a service who were at increased risk of developing breast cancer. This sample may be quite different from a sample of women in the general population. More information is needed regarding the perspective of women at increased risk of developing breast cancer, including women opting for and against genetic testing when available.

What Variables Are Consistently Related to Prophylactic Mastectomy Decision Making?

As noted in the work by Stefanek et al.,¹ a number of variables potentially impact on surgical decision making. This small study of women at increased risk of developing breast cancer found a history of biopsies, subjective risk of breast cancer development, and breast cancer worry to be variables potentially related to an interest in prophylactic surgery. Breast cancer worry differentiated women having this surgery from those interested in the surgery but opting for close follow-up without surgical intervention. This is an area that should draw continuing research interest to assist women in the decision-making process.

Can Psychological Interventions Impact on Variables Possibly Related to Decision Making?

Breast cancer-related worry may be related to the decision to select surgery as a management option. If this variable continues to differentiate women opting for surgery from those deciding against surgery, it may be helpful to assess psychological or counseling interventions that may impact on cancer-related worry and subsequently impact on the decision-making process. In addition, the likelihood of genetic testing availability may well have psychosocial implications for the selection of management options. Studies involving genetic testing for Huntington's disease have noted a variety of psychological reactions among both individuals testing positive and negative for the disease. Even studies noting potential benefits of risk notification also report frequent requests for physical examinations and the need for continued support (26). Of relevance for BRCA1 testing, individuals at risk for Huntington's disease (people with an affected parent) declining testing have demonstrated continuing psychological distress over time at levels greater than individuals testing positive or negative. Obviously, testing for Huntington's disease differs from breast cancer genetic testing in a number of ways, perhaps most notably in the possibility of treatment and cure. However, these findings with Huntington's disease may have decision-making and screening-adherence implications for individuals with a strong family history of breast cancer who tested positive for BRCA1 mutations and those opting against testing.

What Are the Short-Term and Long-Term Sequelae of Prophylactic Mastectomy?

We have very little follow-up information on women completing prophylactic mastectomy. The work discussed in this article indicates that women are quite satisfied with the procedure. However, the follow-up was relatively short, and the surgery was completed with a sample of women receiving strong family and friend support, following counseling at a service for women

at increased risk of developing breast cancer. Women without such support or women not attending services providing counseling for this difficult decision may not report the same level of satisfaction.

How Directive Should Providers Be in Advising for or Against Surgery?

It is clear that physicians can influence breast cancer-screening practices. It is unclear what role physicians play in the decision to have a prophylactic mastectomy versus close follow-up. It is also unclear which subset of women would benefit from a more directive approach addressing the choice of surgery versus close breast cancer-screening follow-up without surgery.

The above list of research questions is certainly not exhaustive. In addition, a number of issues are likely to arise in the near future, including the results of the tamoxifen chemoprevention trial, the degree of success in initiating BRCA1 testing, and any new breast cancer-screening modalities that may be more sensitive and/or specific than current screening tests. Indeed, patients are now faced with a decision somewhat akin to comparing apples and oranges. Specifically, their options include bilateral prophylactic mastectomy versus close breast cancer follow-up without surgery. The former represents a discussion in the context of *prevention* or decreased risk, while the latter discussion focuses on early *detection* of breast cancer. The framing of patient-provider discussion in this way may significantly impact decision making. There are a number of unanswered questions related to the issue of prophylactic mastectomy. It is interesting that many of these questions are also relevant to the issue of prophylactic oophorectomy. This is particularly noteworthy given the recent genetic findings related to BRCA1, mutations of which increase the risk of both ovarian and breast cancers. One area of controversy in the management of women at increased risk of ovarian cancer includes the value of screening both in terms of sensitivity and specificity and increased survival, particularly among premenopausal women (27,28). Other issues include the unproven value of surgery in significantly decreasing the likelihood of cancer development (29,30); the type of surgery recommended, e.g., laparoscopic bilateral salpingo-oophorectomy, total abdominal hysterectomy and oophorectomy, or laparoscopically assisted vaginal hysterectomy (29); and provider perceptions of preventive surgery for women at increased risk of ovarian cancer as a function of family history (31). These areas are in great need of continuing medical and behavioral research.

The issue of bilateral mastectomy as a management option for women at increased risk, including women involved in deciding on BRCA1 testing, will likely remain a critical clinical issue. This does not exclude women opting against genetic testing or women with a strong family history of breast cancer who tested negative on BRCA1 screening. Moreover, discussions of this surgery may increase with further accomplishments in breast cancer genetics. It behooves us to begin to address the questions noted above so that we can adequately care for women at significantly high risk of developing breast cancer.

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Note

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Nutritional Intervention to Prevent Hereditary Cancer

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To determine if the effect of nutritional interventions differs by genetic susceptibility to cancer, we must have both an effective intervention as well as a documented marker of genetic susceptibility. The first large clinical trials to test nutritional intervention strategies have recently been reported, and apparent efficacy has been observed for selected antioxidants in the primary prevention of several cancers, including esophageal, stomach, prostate, and colorectal cancers. At the same time, increasing numbers of markers of genetic susceptibility are being identified. Although susceptibility markers have not yet been evaluated in the context of nutritional interventions in humans, preliminary data in animals indicate that calorie restriction reduces spontaneous tumor mortality in p53-knockout mice. Linking the results from nutritional interventions in humans with markers of genetic susceptibility will allow us to better understand gene-environment interactions. [Monogr Natl Cancer Inst 17:43-47, 1995]

What evidence do we have that nutritional intervention strategies have different effects in individuals who are or are not genetically susceptible to cancer? The following two elements are necessary to answer this question: 1) We must have an effective intervention strategy, and 2) we must have a bona fide marker or markers of genetic susceptibility. At this time, there are no human cancers in which both of these elements have been documented and linked. There are, however, a number of studies that have shown a protective effect for a nutritional intervention, which should enable us to address the question when appropriate models of genetic susceptibility become available. In addition, there is at least one relevant animal model with promising results.

Prevention of Esophageal and Stomach Cancers—the Linxian General Population Trial

In the United States and Europe, the primary causes of esophageal cancer are alcohol consumption and tobacco use and, to a more limited extent, diet. In the areas of the world with the highest risk for this disease (i.e., north central China; north-eastern Iran; southern districts of Transkei, South Africa; and several Asian republics in the former U.S.S.R.), however, the causes appear to be rather different, with diet and unique exposures or practices assuming prominent roles (1). The role of host susceptibility in esophageal cancer has been little studied and is not well understood.

Some of the world's highest incidence and mortality rates for cancer of the esophagus occur in north central China, and the highest Chinese rates are found in Linxian, a rural county in Henan Province (2,3). Historically, in this area, cancers of the esophagus and gastric cardia both have been considered esophageal cancer and, thus, cannot be separated in rate calculations or retrospective analyses. The reasons for the exceptionally high cancer rates in Linxian are not known, but studies during the past 30 years have generated several hypotheses, most prominently dietary, including excessive ingestion of foods that contain factors that may increase risk (e.g., nitrosamine-contaminated fermented and moldy foods) and inadequate ingestion of foods that contain factors that may confer protection (e.g., riboflavin, retinol, carotenes, ascorbic acid, vitamin E, zinc, and molybdenum) (4-7).

Because of its extraordinarily high rates of esophageal/gastric cardia cancer and subclinical deficiencies of several micronutrients among the population, Linxian was selected for a randomized intervention trial to test whether supplementation with multiple vitamins and minerals might reduce the rates of these cancers.

From March 1986 through May 1991, 29 584 adults participated in a nutritional intervention trial in Linxian (8,9). The 40- to 69-year-old subjects were randomly assigned to intervention groups according to a one-half replicate of a 2⁴ factorial experimental design, which enabled simultaneous testing for the effects of four combinations of nutrients: 1) retinol and zinc, 2) riboflavin and niacin, 3) ascorbic acid and molybdenum, and 4) beta carotene, selenium, and α -tocopherol (Factors A, B, C, and D, respectively, in Tables 1-3). Doses ranged from one to two times the U.S. Recommended Daily Allowances (Table 1).

The intervention was successful in improving the micronutrient status of persons who received active agents to levels consistent with well-nourished Western populations, and supplemented groups had significantly better status than nonsupplemented groups (Table 2).

A total of 2127 trial participants died during the intervention period. Cancer was the leading cause of death; 32% of all deaths were due to esophageal or stomach cancer. Significantly lower

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Table 1. Daily doses and types of micronutrients by treatment factor in the general population trial in Linxian, China*

Factor	Micronutrients	Dose/day
A	Retinol Zinc	5000 IU 22.5 mg
B	Riboflavin Niacin	3.2 mg 40 mg
C	Ascorbic acid Molybdenum	120 mg 30 µg
D	Beta carotene Selenium α-Tocopherol	15 mg 50 µg 30 mg

*Adapted from (9).

Table 2. General population trial compliance assessed biochemically over 5-year intervention*

Biochemical assessment					
Retinol, µg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
A	47	35.7 (8.8)	479	54.0 (16.0)	.0001
No A	60	35.5 (13.1)	419	43.0 (14.9)	
Riboflavin (erythrocyte glutathione reductase activation coefficient)					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
B	56	1.73 (0.34)	747	1.19 (0.25)	.0001
No B	51	1.78 (0.40)	745	1.44 (0.31)	
Ascorbic acid, mg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
C	49	0.15 (0.13)	730	0.81 (0.47)	.0001
No C	49	0.25 (0.29)¶	740	0.54 (0.41)	
Beta carotene, µg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
D	47	5.9 (5.5)	443	85.5 (78.5)	.0001
No D	60	6.8 (5.8)	455	12.0 (15.0)	

*Adapted from (8).

†A = retinol + zinc; B = riboflavin + niacin; C = ascorbic acid + molybdenum; D = beta carotene + selenium + α-tocopherol.

‡Base-line nutritional assessment, conducted May 1985; values adjusted for season.

§P values are for *t* tests of factor versus not factor during intervention.

¶P value for "C" versus "No C" at base line = .03.

total mortality (relative risk [RR] = 0.91; 95% confidence interval [CI] = 0.84-0.99; *P* = .03) occurred among those receiving beta carotene-α-tocopherol-selenium supplementation, due

Table 3. RRs for mortality by treatment factor in the general population trial in Linxian, China*

Cause of death	No.	RR by treatment factor†			
		A	B	C	D
Total	2127	1.00	0.97	1.01	.91‡
Cancer	792	0.97	0.98	1.06	.87‡
Esophagus	360	0.93	0.90	1.05	.96
Stomach	331	1.03	1.00	1.09	.79‡
Cardia	253	1.22	1.03	1.07	.82
Noncardia	78	0.59‡	0.94	1.17	.72
Esophagus + cardia	613	1.04	0.95	1.06	.90
Other	101	0.94	1.24	0.98	.80
Cerebrovascular	523	0.99	0.93	1.04	.90
Other	812	1.04	1.00	0.94	.96

*Adapted from (9).

†A = retinol + zinc; B = riboflavin + niacin; C = ascorbic acid + molybdenum; D = beta carotene + selenium + α-tocopherol.

‡*P* ≤ .05.

mainly to lower cancer rates (RR = 0.87; 95% CI = 0.75-1.00) (Table 3). Site-specific mortality was reduced for cancers of the stomach (RR = 0.79; 95% CI = 0.64-0.99) and esophagus (RR = 0.96; 95% CI = 0.78-1.18). Reduced stomach cancer mortality was seen for both cardia (RR = 0.82; 95% CI = 0.64-1.04) and noncardia (RR = 0.72; 95% CI = 0.46-1.14) tumors. Mortality from noncardia stomach cancer among recipients of retinol plus zinc was also reduced (RR = 0.59; 95% CI = 0.37-0.93), based on a total of 78 cases, but this was balanced by an increase in stomach cancer in the cardia (RR = 1.22; 95% CI = 0.95-1.56; *n* = 253 cases), so that there was no overall benefit of treatment with retinol plus zinc on stomach cancer mortality (RR = 1.03; 95% CI = 0.83-1.28). No other significant effects on disease were found for supplementation with retinol and zinc, riboflavin and niacin, or ascorbic acid and molybdenum. Patterns of cancer incidence, based on 1298 cases, generally resembled those of cancer mortality. The findings suggest that vitamin-mineral supplementation, particularly with the combination of beta carotene, α-tocopherol, and selenium, among Linxian adults may reduce total and cancer mortality, due mainly to reductions in stomach and esophageal cancers.

Evidence for Esophageal/Gastric Cardia Cancer Genetic Susceptibility

At least three lines of evidence support the idea that there is genetic susceptibility for esophageal/gastric cardia cancer in high-risk Chinese populations: 1) an association of positive family history with increased risk, 2) evidence of familial aggregation of cases, and 3) segregation analyses suggesting mendelian inheritance in high-risk families.

Evaluation of a positive family history comes from epidemiological studies. In Linxian, China, a family history of esophageal cancer is very common: 32% of participants in the general population trial and 43% of participants in the dysplasia trial (another trial conducted in Linxian among persons at especially high risk of esophageal cancer because they had cytologic

evidence of esophageal dysplasia) reported at least one family member with a history of esophageal or stomach cancer (8). Case-control and retrospective cohort studies in these and other high-risk Chinese populations have shown a consistent association between positive family history and the occurrence of esophageal/gastric cardia cancer, with odds ratios ranging from 1.4 to 7.9 (7,10-12). During the prospective general population trial in Linxian, participants with a positive family history of cancer had a 40% increased risk of developing esophageal cancer (Table 4), and risk increased progressively with the number of affected first-degree relatives (13).

To look for familial aggregation of esophageal/gastric cardia cancer, we determined family history in households in Yangcheng, Shanxi Province, in 1979 and then identified all deaths from esophageal/gastric cardia cancer in selected villages from 1979 through 1989 (14). Only 5% of families with no history of esophageal/gastric cardia cancer in 1979 reported cases by 1989, but 19% of families with a history of esophageal/gastric cardia cancer reported new deaths from this disease over the same time period (Table 5).

Using logistic regression models, segregation analysis was performed on 221 high-risk nuclear families from Yaocun Commune, Linxian, who had at least one affected family member and all offspring older than 40 years (15). Results indicated a

mendelian pattern of transmission, most likely from an autosomal recessive gene with an estimated frequency of 19%. It was further estimated that 4% of the population is predisposed to the development of esophageal cancer as a result of such an autosomal recessive gene. Segregation analysis was also performed in another set of nuclear families from high-risk pedigrees in Shanxi Province, with results again suggesting a mendelian transmission pattern (Bonney G, Hu N, Dawsey SW, et al.: unpublished data).

Linking Intervention Results and Cancer Susceptibility

The Linxian general population trial has shown efficacy for selected antioxidants in the prevention of esophageal and stomach cancers. White blood cells were collected as a source of DNA in more than 6000 participants at the end of the Linxian studies, and other biological samples that might be suitable for DNA analyses (e.g., cytology smears and histology slides) exist on many other trial participants. The future identification of an esophageal or stomach cancer susceptibility gene(s), in combination with continued follow-up of trial participants, will allow comparison of the intervention's efficacy among persons who had or did not have the gene.

Table 4. Odds ratio (OR) for esophageal cancer by family history of cancer in the general population trial cohort from Linxian, China (n = 640 cases)*

Family history of cancer	No. of cases	OR	95% CI
None	360	1.0	—
Any	279	1.4	1.1-1.8
Father	119	1.6	1.3-2.1
Mother	148	1.8	1.5-2.3
Brother	45	1.4	0.9-3.1
Sister	28	1.6	0.8-3.1
No. of first-degree relatives with cancer			
0	377	1.0	—
1	190	1.5	1.1-1.9
>1	70	1.9	1.3-2.7

*Adapted from (13).

Table 5. Shanxi Province familial aggregation study: number of families in study villages with esophageal/gastric cardia cancer deaths from 1980 through 1989 by family history*

	No. of esophageal/gastric cardia cancer deaths per family prior to 1980				
	0	1	2	3	1+
No. of families with esophageal/gastric cardia cancer deaths, 1980-1989	219	41	32	37	110
Total No. of families	4447	251	182	159	592
% families with esophageal/gastric cardia cancer deaths, 1980-1989	5	16†	18†	23†	19†

*Adapted from (14).

† $P < .001$ compared with families with no esophageal/gastric cardia cancer deaths prior to 1980.

Other Intervention Studies—ATBC Cancer Prevention Study

The only other reported nutritional intervention trial large enough to have cancer end points (other than skin cancer) is the Alpha-tocopherol, Beta-carotene Lung Cancer Prevention Study (the ATBC Cancer Prevention Study) (16,17). This study was a randomized, double-blind, placebo-controlled, 2×2 factorial design, primary prevention trial testing the hypothesis that supplements of α -tocopherol (50 mg/day) and/or beta carotene (20 mg/day) can reduce the incidence of lung and other cancers in male smokers. From 1985 to 1993, 29 133 eligible male smokers, 50-69 years old at entry, were randomly assigned to receive active supplements or placebo capsules daily for 5-8 years (median = 6.1 years).

During the trial, 2291 new cancers were identified, including 876 lung, 250 prostate, 155 bladder, 149 colorectal, and 126 stomach cancers; 34% fewer prostate and 16% fewer colorectal cancers were observed in participants who received α -tocopherol compared with those who did not (Fig. 1). Whole blood collected from more than 20 000 participants near the end of the trial will permit research on the relationship of genetic susceptibility markers and intervention effects, both beneficial as well as harmful (e.g., the unexpected finding of increased lung cancer risk among participants given supplements of beta carotene). As examples, the MSH2 and MLH1 polymorphisms (on chromosomes 2p16 and 3p21, respectively) that have been associated with hereditary nonpolyposis colorectal cancer could be evaluated in relation to the efficacy of α -tocopherol for colorectal cancer.

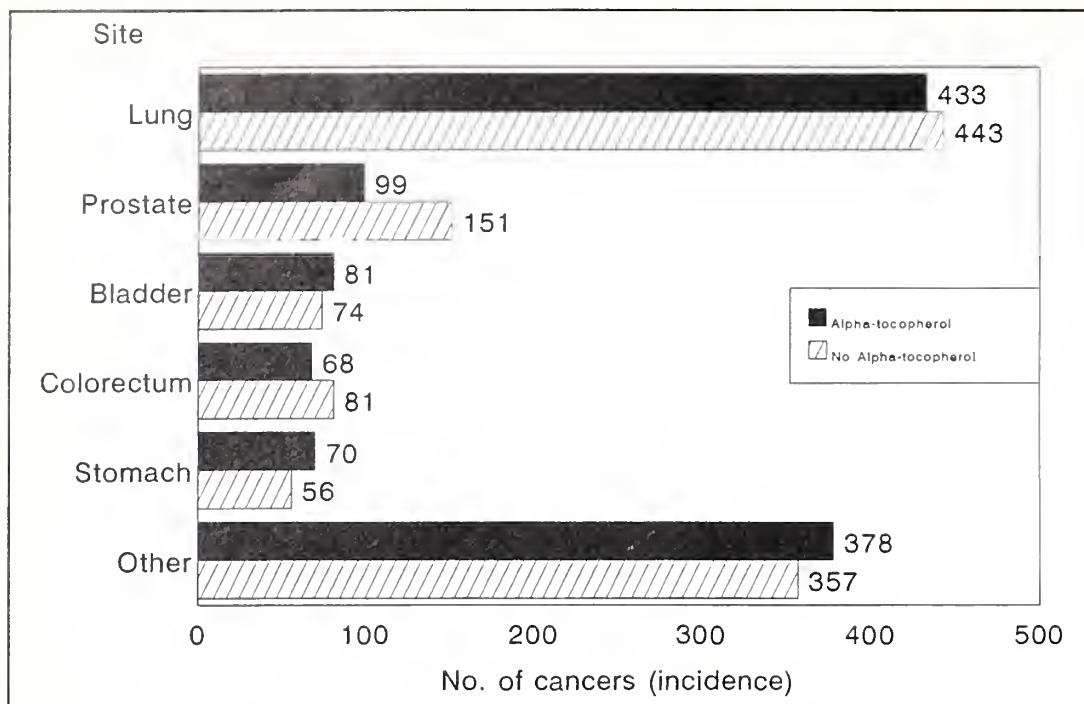


Fig. 1. Incident cancers by α -tocopherol treatment in the ATBC Cancer Prevention Study. Excludes nonmelanoma skin cancers. Adapted from (17).

Animal Models

An exciting new transgenic animal model using p53-knock-out mice (in which both alleles of the p53 tumor suppressor gene are inactivated by gene targeting) has recently been used to test cancer prevention strategies. In one such study, tumor development in response to calorie restriction was evaluated (18,19). Mortality from spontaneous tumors was 100% by 28 weeks in the mice fed ad libitum, but it was only 57% in mice restricted to 60% of the ad libitum calorie level. Furthermore, multiple tumors were present in 34% of the mice fed ad libitum but in only 16% of the calorie-restricted animals by 28 weeks (Table 6). Although all the p53-knockout mice in both groups died by the end of the study (48 weeks), median survival was significantly longer in calorie-restricted animals compared with animals fed ad libitum (25 versus 16 weeks). Although results from this experiment are not directly relevant to humans, the delay in tumor onset observed in calorie-restricted mice supports the general notion that dietary manipulation can be beneficial even in the presence of strong genetic susceptibility.

Table 6. Spontaneous tumorigenicity in p53-knockout mice fed ad libitum or fed calorie-restricted diets*

Calorie group	Mortality from tumor, 28 wk, %	Multiple tumors, 28 wk, %	Mortality from tumor, 48 wk, %	Median survival, wk
Ad libitum (n = 30)	100	34	100	16
60% calorie restricted (n = 28)	57	16	100	25

* Adapted from (18,19).

Summary/Conclusion

The recent demonstration of efficacy for nutritional interventions in several large cancer prevention trials and the rapidly expanding number of molecular genetic markers offer, for the first time, the exciting and unique opportunity to examine intervention effects according to genetic susceptibility status. Preliminary data in animals suggest that nutritional intervention can be efficacious in genetically susceptible rodents. Targeting effective nutritional intervention approaches to high-risk populations identified by genetic susceptibility markers may be an important new strategy in cancer control.

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Cancer Chemoprevention

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A new direction for cancer prevention and control is chemoprevention, defined as the use of specific natural and synthetic chemical agents to reverse or suppress carcinogenesis and prevent the development of invasive cancer. The chemopreventive approach depends on the ability of certain chemical agents to block mutagenesis and control cellular differentiation and proliferation in epithelial tissues. Support for the chemopreventive approach is based on the biologic concepts of field cancerization and multistep carcinogenesis, as well as the clinical efficacy already shown by agents such as retinoids and tamoxifen in reversing premalignancy and preventing second primary tumors. Although chemoprevention is not yet established as a standard therapy, the results of reported trials are very promising and have raised tremendous interest in this strategy for cancer prevention. The development of more effective, less toxic chemopreventive agents remains a high priority in furthering the use of this clinically valuable approach to the prevention and control of cancer. [Monogr Natl Cancer Inst 17:49-53, 1995]

Chemoprevention Perspectives

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy, and this constitutes one of the foremost new investigative approaches for controlling epithelial cancer. Recent advances in our understanding of the molecular and genetic mechanisms of carcinogenesis have generated tremendous enthusiasm for this method's potential impact on reducing cancer risk in humans (1-7).

Significant advances in chemoprevention have been made in the past decade (Table 1). These advances include identification of effective chemopreventive agents, such as 13-*cis*-retinoic acid (13cRA), tamoxifen, and sulindac; implementation of large-scale human cancer prevention clinical trials; and establishment of screening systems for the identification of chemopreventive agents. To date, more than 2000 agents from more than 20 chemical classes have shown preclinical chemopreventive activity; the National Cancer Institute (NCI) currently sponsors more than 40 clinical chemoprevention trials throughout the world.

The first of the two basic theories on which chemoprevention of epithelial carcinogenesis is based is that of the multistep carcinogenic process (2,3), which states that premalignancy is one of a series of progressive stages that can be reversed with effective chemopreventive approaches. The second theory is that of

field carcinogenesis, which underscores the need for systemic treatment to address exposure to carcinogens throughout a tissue field, such as the aerodigestive tract. These concepts are strongly supported by laboratory data from many epithelial carcinogenic systems. The chemopreventive approach can be applied to individuals at increased risk for cancer development, to individuals at high risk for the development of second primary tumors after having been rendered apparently free of initial disease, and to individuals with inherited susceptible genes that predispose them to develop cancer (e.g., Li-Fraumeni syndrome, BRCA1 families, and individuals at risk for hereditary breast, ovarian, or colon cancer).

Much of the rationale for early clinical chemoprevention trials came from epidemiologic data suggesting the existence of dietary inhibitors of carcinogenesis (6). It is not possible, however, to determine from epidemiologic studies which specific chemicals within the diet provide anticarcinogenic effects. Laboratory studies have identified more than 2000 chemicals with the ability to suppress carcinogenesis in various animal models. However, carcinogenesis and chemoprevention studies in animals may not translate directly to effects in humans. Controlled clinical trials are required to establish the chemopreventive activity of promising compounds in humans. Over the last 5 years, randomized studies have demonstrated significant chemopreventive activity for several agents, including retinoids in head and neck, lung, skin, and cervical carcinogenesis; tamoxifen in breast carcinogenesis; and sulindac in colon carcinogenesis (2-18; Table 1). These clinical advances have been paralleled by major basic science advances in the molecular biology of carcinogenesis and the mechanisms of chemopreventive agents.

How do chemopreventive agents work? Some chemopreventive compounds act by changing the pathway of cells from proliferation to differentiation. Some compounds directly bind carcinogens and/or enhance metabolism of the carcinogen into inactive forms, and others induce programmed cell death. A great deal has been learned recently about cellular differentiation, regulation of cell proliferation, growth factors, and other mediators of the transformation of normal cells to malignant cells (1-5).

As a result of the increasing interest in chemoprevention, many new agents have been developed and are in various stages of evaluation for possible use in human subjects. The retinoid

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Table 1. Positive randomized chemoprevention trials

Investigator(s) (Ref. No.)	Status	Agent*	No. of patients	Results
Hong et al. (8)	Oral leukoplakia	13cRA	44	Reversal of oral leukoplakia
Hong et al. (9)	Head and neck cancer	13cRA	103	Reduction of second primary tumors
Stich et al. (10)	Oral leukoplakia	Vitamin A	54	Reversal of oral leukoplakia
Han et al. (11)	Oral leukoplakia	4-HPR	61	Reversal of oral leukoplakia
Chiesa et al. (12)	Oral leukoplakia	4-HPR	80	Prevention of new oral leukoplakia
Lippman et al. (13)	Oral leukoplakia	13cRA, β-carotene	24 29	13cRA was more effective for maintaining reversal of oral leukoplakia
Moon et al. (14)	Actinic keratoses	Retinol	2298	Decrease in squamous skin cancers
Pastorino et al. (15)	Lung cancer	Retinyl palmitate	307	Reduction of tobacco-related second primary tumors
Meyskens et al. (16)	Cervical dysplasia	Tretinoin	301	Reversal of moderate dysplasia
Blot et al. (17)	Geographic high risk	Multiple vitamins/ minerals	29 584	Reduction in gastric cancer incidence
Giardiello et al. (18)	FAP†	Sulindac	22	Prevention of colon polyposis

*4-HPR = fenretinide.

†FAP = familial adenomatous polyposis.

13cRA is one of several chemopreventive agents that has achieved significant results in small, randomized clinical trials. Currently, several large, randomized, placebo-controlled trials of 13cRA are being conducted in patients with both head and neck and lung cancers.

The mechanism of retinoid activity in reversing oral carcinogenesis, as well as cervical carcinogenesis, is under intensive investigation, and studies in this area have produced very promising results. Recent studies (19,20) have indicated that retinoic acid receptors (RARs) play a major role in head and neck carcinogenesis; in particular, the expression of RAR-β is significantly reduced as tissue progresses toward carcinoma in both head and neck and lung cancers. Furthermore, 13cRA treatment in patients with oral premalignancy significantly up-regulates RAR-β expression, with correlation between upregulation of RAR-β and clinical response. Therefore, RAR-β is an excellent candidate for an intermediate end point for retinoid chemoprevention trials.

Chemoprevention shows enormous promise for reduction of the rates of both the morbidity and mortality of cancer. Recent insights into the molecular and genetic mechanisms of the carcinogenic process have provided the conceptual framework for this approach. The next step in the evolution of chemopreventive approaches is the development of intermediate biomarkers, and this area is under intensive study. Validated intermediate end points could reduce phase III trial populations, durations, and costs. The future of chemoprevention will largely be determined by several ongoing phase III studies, including trials of retinoids in head and neck and lung cancers, tamoxifen and fenretinide in breast cancer, and finasteride in prostate cancer (Table 2).

Ongoing Chemoprevention Trials: Nature and Design Elements

Although phase I-III chemoprevention trial designs parallel those of chemotherapeutic trials, there are significant differences (2). Promising new agents from preclinical and epi-

demologic studies are first tested in humans in short-term phase I studies to determine toxicity. The goal of phase I chemoprevention trials is to establish an effective agent dose that produces no more than mild toxicity in the majority of patients. This differs from the end point of phase I chemotherapy trials, which is to establish the standard maximum tolerated dose. After the phase I toxicity screening, a short-term phase II trial is conducted to establish whether the agent affects one or more intermediate end points. Two types of phase II trials are conducted. Phase IIa studies are preliminary assessments of biomarker modulation and feasibility of biomarker study techniques, and phase IIb trials are definitive, randomized assessments of intermediate end point modulations. The sample size for phase II trials depends on the number of subjects needed to make a statistical distinction of change in the intermediate end point of the study. This resembles the study design used in phase II chemotherapy trials, which depends on the statistical needs to detect target cancer response rates. Placebo-controlled phase II trial designs are unique to chemoprevention. They are, however, critical, since intermediate end point markers, unlike established advanced cancers, can spontaneously regress. After the short-term activity is established through phase II trials, phase III trials are conducted to establish long-term efficacy in reducing cancer incidence and to validate promising intermediate biomarkers. Phase III trials can require thousands of subjects and 5-10 or more years to complete (Tables 2 and 3).

Two major issues in chemoprevention are the need for long-term intervention and the potential for long-term toxicity. The ultimate trial end point is incidence of cancer, whether primary or secondary. Demonstrating the specific differences in occurrence of this ultimate end point requires many years of study with large populations, which makes phase III trials very expensive. Variant designs with this end point, such as factorial designs, can reduce costs by allowing the randomized testing of more than one agent to achieve more than one prevention goal within the same phase III population.

Table 2. Selected ongoing chemoprevention trials*

Cancer site (No. of trials)	Risk group	Inhibitory agent†
Breast (3)	Women age 60 or older, women of equivalent or higher risk	Tamoxifen
	Proliferative breast disease	Tamoxifen
	Stage I breast cancer	4-HPR
Cervix (7)	All women	β -carotene (2 trials), 4-HPR, DFMO
Prostate (2)	Men with stage A1, age 50 or older	Finasteride
	Prostate specific antigen >4	4-HPR
Bladder (2)	Persons with resected superficial tumors	4-HPR, DFMO
Colon (11)	Previous colon adenoma	Calcium-based treatment \pm fiber, β -carotene, ascorbic acid, α -tocopherol (vitamin E), DFMO, fiber supplement, sulindac
	Previous colon polyp	Calcium-based treatment
	Familial adenomatous polyposis	Sulindac
	High-risk individuals	Calcium-based treatment
	Dukes' stage A & B1	Omega-3 fatty acids
	Previous colon cancer	β -carotene
Lung (4)	Cigarette smokers, asbestos exposure (men), asbestosis	β -carotene, retinol
	Cigarette smokers	13cRA
	Cigarette smokers (women)	β -carotene, vitamin E
	Stage I non-small-cell lung cancer	13cRA
Head and neck (3)	Oral leukoplakia	β -carotene and retinyl palmitate, 13cRA
	Head and neck cancer	4-HPR, 13cRA, β -carotene
Head and neck and lung (1)	Head and neck and lung cancers	NAC, retinyl palmitate
Skin (3)	Albinos in Tanzania	β -carotene
	Previous basal cell carcinoma	β -carotene
	Actinic keratosis	Retinol
All cancers	Physicians, no risk specification	β -carotene, aspirin

*Information from the NCI Chemoprevention Branch.

†4-HPR = fenretinide; DFMO = 2-difluoromethylornithine; NAC = *N*-acetylcysteine.

Biomarkers and Intermediate End Points

Intermediate end points are clinical, histologic, biochemical, and molecular biomarkers that can detect early, specific carcinogenic changes, which ultimately may prove to correlate significantly with carcinogenic reversal or progression. The selection of biomarkers for chemoprevention trials is based on four major criteria: marker studies can be performed on small tissue specimens, the marker is expressed differently in normal versus high-risk sites, it is subject to modulation by specific agents, and it has a low rate of spontaneous change (2). Many methodologic issues in this field are yet to be resolved. These include the acquisition and handling of specimens, sampling errors, cost, sensitivity/specificity, and quality assurance/control. In addition to the identification of specific markers, we also require better techniques for their study. In particular, there are major financial, logistic, and technical difficulties in the study of molecular markers as intermediate end points for chemopreven-

tion trials. These and other issues discussed above must be resolved before intermediate end point biomarkers are to have an established role in new chemopreventive drug development strategies.

Biomarkers and intermediate end points are important in the field of chemoprevention in two ways. First, as predictors of increased risk, they help identify individuals who are likely to develop cancer and for whom intervention trials are justifiable. Second, they can be used as cost-effective measures for assessing the efficacy of chemoprevention in a relatively short period of time. The development of reliable, accurate biomarkers will facilitate assessment of individual risk and efficacy of new strategies to prevent cancer development.

If biomarkers and intermediate end points are validated as predictors of certain cancers, they can provide scientific tools for the design of reasonable, cost-effective chemopreventive intervention trials in which biomarkers and intermediate end points are used rather than the development of malignancy. Intervention trials that use biomarker modulations as the study end points will be completed in a relatively short period of time and will require fewer patients, with more reasonable costs.

The most-studied intermediate biomarkers in chemoprevention to date are nonspecific indicators of genotoxicity, such as micronuclei and abnormal proliferation (2). These two biomarkers can reflect fundamental aspects of carcinogenesis, cellular mutation through genotoxic markers, and hyperproliferation as a proliferation marker. Micronuclei and proliferation marker studies illustrate the major current problems with the design and interpretation of biomarker studies. Elevated

Table 3. Major negative NCI randomized chemoprevention trials

Site	Agent(s)	No. of patients	Reference No.
Lung	α -tocopherol, β -carotene	29 133	(22)
Skin	β -carotene	1805	(25)
	13cRA	981	(26)
Colon	Aspirin	22 071	(27)
	β -carotene, vitamin C, vitamin E	864	(28)
Esophagus/stomach	Vitamins, minerals	3318	(29)

micronuclei counts in oral leukoplakia and increased proliferation marker patterns in the colon are consistent findings in high-risk individuals. Many studies have, however, indicated problems with both of these markers. Substantial modulation of micronuclei formation by chemopreventive agents (21), for example, does not relate to suppression or progression of carcinogenesis (22). Many of these problems may be due in part to sampling errors or random marker changes.

Currently, many investigators are trying to identify highly specific markers at the molecular level, growth-regulated genes, and other more sensitive markers. Mutations of p53 are a biomarker of an early stage of carcinogenesis in the upper aerodigestive tract and skin and of later stages of carcinogenesis in the colon and bladder (23). Accumulation of p53 protein increase in direct association with histologic progression in upper aerodigestive tract and lung carcinogenesis (23). Furthermore, an inverse relationship between p53 protein levels in tissue and response to 13cRA in oral premalignancy has been observed (24). RAR- β is lost in the early stages of head and neck carcinogenesis and is upregulated with retinoic acid treatment, although no data are available so far regarding the correlation between RAR- β upregulation and prevention of head and neck cancer.

Summary and Future Directions

Chemoprevention is a promising new strategy for reducing the rates of cancer morbidity and mortality. Clinical studies have shown that certain agents have significant activity in reversing oral, colon, and cervical premalignancy, in preventing primary skin and stomach cancer, and in preventing second primary tumors associated with head and neck and lung cancers (Table 1). Retinol has prevented squamous cell carcinoma in patients with actinic keratosis, but not in patients with prior skin cancers. In China, the combination of beta carotene, vitamin E, and selenium has prevented gastric cancer in high-risk subjects without dysplasia, but not those with dysplasia. Sulindac has suppressed colon polyp development in high-risk subjects. Tretinoin has reversed moderate but not severe cervical dysplasia. Several important negative phase III trials have also been published recently (Table 3).

Many other randomized trials currently under way will help determine the future of chemoprevention. Early studies of the biology of carcinogenesis provided a strong rationale for conducting biomarker-integrated chemoprevention trials with intermediate end points. Molecular markers of human epithelial premalignancy continue to provide potential new biomarkers for future studies. Aneuploidy, DNA adducts, p53 mutations/protein accumulation, 9p loss, ras mutations, RAR- β , and differentiation antigen are some of the most promising of these new biomarkers. Biomarker studies currently provide valuable insights into the carcinogenic process and help select new agents from phase I and II trials for testing in large-scale phase III trials that use the definitive end point of cancer incidence. In the future, validated biomarkers can replace cancer incidence as the end point for these large-scale, definitive chemoprevention trials, thereby reducing tremendously the time and resources required.

An important laboratory finding in a recent clinical retinoid trial is the relationship between the two families of retinoic acid receptors—RARs and RXRs—and the anticarcinogenic mechanism of retinoid action. Recent work by our group identified the RAR- β receptor as an important link in the progression of oral premalignancy and in the reversal of the process by retinoids. High levels of accumulation of p53 protein in oral premalignancy is associated with retinoid resistance. Although not yet accepted as standard clinical practice, chemoprevention has many basic and clinical researchers excited about its potential contribution to cancer prevention and control.

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Minority Inclusion in Clinical Trials Issues and Potential Strategies

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Inclusion of all elements of our diverse society in clinical trials is desirable for scientific, ethical, and social reasons. Inclusion in scientific study becomes more important as genetic discovery increases and implications for diagnosis and screening become even more specific to the individual. Minority recruitment involves marketing and public relations as well as science. Efforts at minority inclusion in clinical study are as much a matter of sociology as they are of study design.

The term "minority" is often defined by race, socioeconomic, geography (rural versus urban), ethnicity, culture, or sex. A common theme among these definitions is people who do not understand the value of clinical trials, are apprehensive about entering clinical trials, or have concerns conflicting with participation in clinical trials. Minority individuals often feel that they are the most vulnerable. In this article, the term "minority" refers to race and ethnicity, such as blacks and Hispanics, and to the poor (including poor whites). Poor whites are the least-mentioned minority in the literature and may be the "most forgotten minority."

This paper addresses the importance of minority inclusion in clinical studies, describes some common views and concerns of those who have been underrepresented in large clinical trials, and outlines strategies that may be useful in recruiting minorities to clinical studies. Few have formally studied minority accrual to clinical studies and especially to screening and descriptive studies that do not involve treatment of a symptomatic illness. For that reason, much of this discussion is in a sense anecdotal, drawn from interviews with clinical investigators and data managers involved in accrual of black, Hispanic, and poor whites to the National Cancer Institute's Minority-Based Community Clinical Oncology Program (MBCCOP). In 1990, the National Cancer Institute funded 10 MBCCOPs specifically to provide minority communities with greater access to clinical trials.

Importance of Diversity in Trials

Diversity of the population sampled or a representative biopsy increases the scientific validity and generalizability of research results (1-3). Heterogeneity in clinical trials is also an ethical issue. When a new therapy or intervention is well understood in one population and in the health care system in which that population receives care, but not understood in other populations and other health care environments, medical science has failed the society it is supposed to serve. Likewise, in genetic and other descriptive studies, when a finding is known to be true in one population and not in others, medical science fails to serve all of society. In a sense, broad-based inclusion of minorities in clinical trials is also a civil rights issue and a

sociopolitical issue. The recent National Institutes of Health (NIH) Revitalization Act of 1993 (Public Law 103-43) mandates inclusion of minorities in clinical trials and outreach to minority communities (4).

There is a growing literature showing the importance of sex, race, ethnicity, and culture in health, the seeking of health care, and treatment. However, relatively little information currently exists to show that there are significant genetic differences by race, ethnicity, or culture relating to the etiology of major cancers. The potential for genetic differences or differences in response to an experimental intervention exists as we find more familial and inherited traits specific to certain families. This should be realized early and looked for in clinical studies. It is far better that differences be investigated in prospective fashion rather than discovered after years of anecdotal reports.

Racial and sex differences in response to medical interventions have been noted and are not always trivial and biologic. For example, after years of anecdotal reports, it is now well established that certain types of antihypertensive drugs, such as beta blockers and inhibitors of angiotensin-converting enzymes, are less effective in African-American men when compared with white men (5,6). The need for heterogeneity in trials actually expands far beyond race, sex, or ethnicity. Indeed, drug kinetics can be different in individuals, even within the same race, and this in itself justifies diversity in drug trials beyond factors or such factors as race and ethnicity. There is no known racial or ethnic link to acetylation, and fast acetylators have a different response to certain drugs when compared with slow acetylators.

Another important aspect in therapeutic trials is that treatments tested may have favorable outcomes in certain clinical environments but not in others. Cancer centers with specialized staffs and equipment may be able to consistently reproduce the results of a trial, whereas community or public hospitals may be unable to do so. This can be seen very easily if a study has a heterogeneous population of participants and institutions.

Barriers to Minority Accrual

There are numerous so-called "barriers" to minority accrual in clinical trials. Some barriers involve distrust and misunder-

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standing of the medical and scientific community and some involve logistic and economic concerns. Many minorities have very legitimate concerns discouraging participation. These concerns are often not obvious to the medical community and are very different from the concerns of majority America.

Numerous minority groups generally view American health care and especially medical research with great suspicion. This may partly be due to the paranoia that normally comes with not being in the empowered majority, but the history of medical research is such that it is not always an unreasonable view. There have been a number of deceptions in medicine in which vulnerable people have been taken advantage of. These unfortunate events fuel doubt and fear of being "used" for the investigators' gain.

The legacy of the Tuskegee Syphilis Study is often cited as "the primary reason" why African-Americans do not enter clinical trials. The study began in 1932 and enrolled 400 African-American men (7,8). These men were not well informed that they were on a clinical trial and they were observed and untreated even after the availability of a reasonable therapy, penicillin. A Senate investigation disclosed the existence of the trial in 1972, and it was closed 40 years after it started.

The Tuskegee Syphilis Study and its history are well known in African-American communities. It may not be, however, the major reason why blacks and other minorities are hesitant to be involved in medical research. Many individuals have personally experienced abuses while in hospitals and clinics. The American medical system that minority patients see is often one in which physicians and nurses frequently do not have the time to deal with people. Abrupt answers and hurried, insensitive handling are relatively minor abuses that create a lasting negative impression and fuel suspicion of medicine.

A special issue in some Hispanic and African-American cultures is a sense of fatalism. Some people believe they have no control over their futures. These people feel medicine offers little hope, so they do not seek medical help and will not volunteer for participation in a study (9).

The lay media often add to the problem of skepticism by creating tremendous confusion, even among nonminority patients. There are frequent reports that research has found a wonderful treatment one week and that it is useless or harmful the next week. There are numerous reports of scientific breakthroughs that have tremendous promise, yet minorities never see the fruits of these breakthroughs. This creates a great deal of skepticism and cynicism.

Attempts to increase minority participation may actually have the opposite effect. Efforts to reach out, inform, and recruit to clinical trials can scare people away from trials. Full disclosure in lengthy, hard-to-read consent forms, while necessary, can be intimidating and overwhelming. Certain terms and phrases also discourage participation. For example, "genetic screening" or "genetic testing" are especially disturbing phrases to African-Americans. "Genetic" has often been used by individuals to insult and degrade African-Americans. Recent publicity about books like *The Bell Curve*, intended or not, will not help those trying to accrue genetic studies. Even legislation to open trials to all can cause potential study participants to be suspicious. The NIH Guidelines on the Inclusion of Women and Minorities as

Subjects in Clinical Research (10) increases pressures on physicians to recruit minorities to clinical trials. These guidelines and the law behind them may cause some patients and potential trial participants to question the motivation of even the most well meaning of physicians. Patients will ask themselves if the physician offering participation in the trial is interested in filling a quota or in the patients' best interest.

Being in a minority and being impoverished is frequently synonymous. The burden of poverty is high and often leads to tremendous neglect of nonemergent medical needs (11). There are many pertinent and pressing concerns. Common barriers to obtaining even necessary medical care include the following: language, cost, transportation difficulties, inconvenient clinic hours, lost wages, and child-care difficulties (12,13). The norm for these patients, be they white, black, Hispanic, or other, is fragmented health care. Health maintenance and disease prevention is not among the daily priorities of life, and voluntary participation in clinical studies is a very low priority. It should not be surprising that accrual of healthy minority applicants to screening and prevention trials is far more difficult than accrual to trials treating specific illnesses.

Accrual to Treatment Trials

The MBCCOP has provided an opportunity to study accrual to clinical trials. Analyses have shown that minority patients will enter clinical treatment trials in proportions similar to majority patients when treated in the appropriate environment (14,15).

Over a 2-year period, 151 doctors in these programs kept a log of all newly diagnosed cancer patients. Data collected included date of diagnosis, patient age, race/ethnicity, primary cancer diagnosis, stage of disease, availability of a protocol for the specific cancer site, clinical eligibility for the protocol, and, if a trial was available, whether the patient entered the trial.

Of 3585 cancer patients, 19.3% were Hispanic, 46.7% were African-American, and 28.4% were white (16). Patients of other races or ethnicities composed 5.6% of the study. Of these patients, 420 were eligible for clinical trials and 247 entered a clinical trial. Approximately one third of all eligible patients choose to go into trial, be they black, white, Hispanic, or other. Among these patients, race or ethnicity did not appear to influence participation in clinical treatment trials. This suggests that African-American, white, and Hispanic patients, who have access to clinical treatment trials in the proper environment, enter those trials at similar rates. This finding is important because many health care providers have said that they do not discuss or offer clinical trials to minorities on the assumption that they are unwilling to enter trials (17).

The MBCCOP findings concern cancer patients being recruited to clinical treatment trials. These individuals are patients already in a referral network who have relationships with physicians and are referred to other physicians participating in clinical research. They have a disease and need a treatment. Findings may be different when recruiting healthy individuals who are outside of the usual referral network for people with cancer.

Recommendations

Heterogeneity can be obtained only through making the existence of trials known, available, and convenient to all facets of the American population. We must communicate why the questions we are studying are important to their community. This requires an extensive educational effort for ourselves as well as for the public we serve. The mistrust and skepticism that community members have must be overcome. Studies conducted by people who move into a community in which they have never been before and have never known before may be doomed to low accrual. Individuals and institutions with a history of service to the community are far more likely to be successful.

Those of us who design trials must know our target populations, their unique history, their unique needs, and their concerns. For example, the history and needs of black populations in Virginia may be very different from black populations in Alabama or Louisiana. Removal of barriers to participation is of paramount importance to minority inclusion. A community advisory board can often identify the barriers unique to a particular community (18). Investigators should involve the community in planning trials by consulting local community leaders, ministers, politicians, labor leaders, and physicians. In the African-American community and in many others, the cooperation of local ministers requires only personal contact by the study leader and a good explanation of the importance of the study.

The importance of a specific trial or study may best be communicated by addressing audiences at community centers, social groups, union halls, and churches. This has been very successful for some cancer-screening studies. Information at these meetings can be disseminated through trusted local spokespersons and respected figures who understand the trial and the social and scientific needs of the community. Endorsements from sports figures and popular politicians can be very helpful. Coverage by local television and radio as well as in local newspapers can also be helpful. While the media are frequently more interested in publishing results of clinical trials rather than discussing what trials are ongoing, there is some interest in new trials. Small community newspapers may be more willing to spend time discussing trials involving diseases of relevance to their readership.

On a personal level, staff sensitivity and knowledge of specific cultural and social characteristics of the individual are imperative. Subjects/patients should be addressed in the language and manner of their preference. Individuals in some cultures are offended by being called by their first name. It must be clear at all times that the individual's dignity and autonomy are respected. Staff must speak candidly and avoid any sense of coercion. One should not oversell or suggest that nonparticipation is foolish. Potential subjects should be encouraged to discuss participation with family, friends, and other respected individuals.

Conclusion

Heterogeneity is important if the findings of clinical research are to be generalizable. Heterogeneity can include involvement of people from diverse races/ethnicities and socioeconomic backgrounds but involves even more diversity. There will always be difficulty accruing subjects to research studies from all facets of society, but it is worth the effort. Minorities and indeed all people are more likely to consider and enter trials when the trial has relevance to them, their family, and their community. A carefully planned strategy, recognizing the characteristics and culture of the target populations, is necessary. This strategy must involve a plan to communicate the importance and availability of the study and a plan to bring the community opinion leaders as well as potential patients/subjects into contact with the investigators.

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Physician Responsibility in Conducting Genetic Testing

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The rapid growth of DNA-based tests raises complex questions about how to integrate them efficiently into clinical medicine and about the medicolegal consequences of rapidly shifting standards of practice. Standards of practice change in response to many factors; the most important are guidelines promulgated by professional bodies or published comments by opinion leaders, malpractice litigation, and legislation. Recently, human geneticists have successfully shaped the clinical use of tests for Huntington's disease and carrier screening for cystic fibrosis. Clinical geneticists, oncologists, and others should work together now to develop practice standards for the use of new DNA-based predictive tests for breast, colon, and other cancers. [Monogr Natl Cancer Inst 17:59-61, 1995]

My assignment is to provide you with an overview of physician responsibility in genetic testing. In essence, I will review from a medical and legal perspective how standards of care are set in our society. Although I will be discussing physicians, my comments are generally relevant to all health care professionals. Most of the relevant legal precedents do not involve genetic tests but derive from analogous situations.

There are at least three criteria one would like to see met by a particular genetic test before even beginning a discussion about whether a physician should suggest that it may be of help to a patient: (a) it must have undergone clinical validation, (b) experts must have reached consensus as to how to determine who is an appropriate candidate for the test, and (c) it must be clear that physicians or other health care professionals have the ability to properly inform patients about the test and to provide adequate genetic counseling (1).

Medicolegal Comments on Setting Standards of Care

I should like to make a few general observations about standards of care. First, they are ever changing, always responding to clinical advances. Second, although not so dramatically as was the case 30 years ago, standards of care may differ from state to state. Third, it is important to understand that from a legal perspective the level of performance expected of any particular physician is only that he or she do what is expected of the average reasonable clinician.

The standard of care with regard to genetic testing is evolving. For example, a three-marker (alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol) test is rapidly

replacing the alpha-fetoprotein test to ascertain women at increased risk of carrying a fetus with a neural tube defect. This is because the three-marker test is an effective means to identify women (regardless of their age) who are at increased risk of carrying a fetus with Down syndrome. Among human geneticists, there is also an ongoing debate about the role of fluorescent in situ hybridization technology in prenatal medicine. Another hotly debated topic is the proper use of Fragile X testing in screening children with unexplained development delay. In 1988, if one had asked a group of pediatric neurologists whether such children should routinely be tested for Fragile X syndrome as part of their work-up, opinions would have diverged widely. In 1994, a strong majority would answer in the affirmative, i.e., that the Fragile X test should be a standard element in the routine work-up of such a child. What drove the change? The cloning of the gene, the development of DNA-based testing, and a growing appreciation for the high prevalence of the disorder.

How do standards of care evolve? They ripen as the relevant physician community becomes aware of a new technology. It does not happen overnight, and it does not happen just because an article appears in a prestigious journal. The preferred way is by clinical consensus. One example is the evolution of laparoscopic surgery, a technology that was introduced rather quickly into surgery. Today, it is widely used, but it has not replaced open upper-right quadrant surgery. The newer surgery is now an acceptable alternative in some situations.

Guidelines promulgated by medical societies are very important. For example, in 1989 just after the cloning of the gene for cystic fibrosis (CF), the American Society of Human Genetics issued a strong statement asserting that it was not yet time to engage in mass population screening for CF carriers (2). In effect, the statement set a standard of practice that opposed mass screening.

In 1991, a workshop convened by the National Institutes of Health developed a detailed set of suggestions that constituted guidelines for CF screening. The published document was endorsed by the American Society of Human Genetics (3). One key suggestion, that it would be helpful to study pilot CF screening programs before launching a national effort, led to a decision by the National Center for Human Genome Research to fund such studies. In 1995, 6 years after the cloning of the CF gene, there has yet to be any large-scale screening in the United

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States. In effect, the advice of professional groups has kept the lid on wide-scale clinical application of screening.

A second, all too common, way in which a standard of care evolves is in response to litigation. Typically, an individual who believes he or she has been harmed by a breach of a standard of care challenges a doctor's conduct, is victorious at trial, and is upheld on appeal. If just a few appellate courts in a few states resolve similar cases in the same way, they may in effect judicially impose a standard of care of national proportions. During the late 1970s, a number of lawsuits helped to create a standard of care that physicians caring for pregnant women who would be 35 years of age at delivery must inform them of the age-associated risk of carrying a fetus with Down syndrome and of the availability of amniocentesis and karyotyping to investigate this possibility.

A third way in which standards of practice are constructed is through legislation or government regulation. For example, mass newborn screening, by far the largest use of genetic tests, is legislatively mandated in every state. Regulations, rules issued by states or federal agencies that have the force of law, affect standards of care in many ways. Perhaps the most controversial federal regulation during the 1980s was the so-called "gag rule," which forbade physicians, nurses, or other providers working in federally funded family planning clinics to even mention abortion. The "gag rule" was repealed by an executive order signed by President Clinton soon after he took office. During the years it was in force, however, it tended to deprive poor women from being fully informed about possible pregnancy outcomes (such as the increased risk of Down syndrome in fetuses conceived by older mothers), in effect creating a lower standard of care than existed in the private health care sector.

With regard to developing a standard of care for predictive testing in cancer, oncologists have an opportunity to act prospectively to develop rational standards of practice and to help the medical community and the public come to grips with the new technology. I suggest that appropriate professional groups move quickly to develop and publish such guidelines. The leaders of such an effort should seek the widest possible consensus. If different professional groups issue conflicting guidelines, clinicians will be in a quandary.

With the proliferation of new genetic tests, physicians need explicit guidance on how to introduce them into clinical practice. Such guidelines may also be useful in patient education. For example, physicians may rely on them to help dissuade persons from inappropriate testing.

Guidelines do not eliminate liability risk, but they do reduce it. Practice guidelines also help to make the pace of change reasonable. It should be noted, however, that once articulated, a standard of care, however conservative, can constitute a formidable legal weapon to use against a physician who fails to measure up to it.

A standard of care that asserts it is not yet time to offer a new test does not necessarily insulate physicians from the argument that a patient should be informed about its existence. Physicians may have a duty to inform patients about a test even if they do not recommend it. Furthermore, aggrieved patients may initiate a lawsuit even if it has relatively little legal merit.

Predictive Testing in Cancer

I want to discuss briefly the impact that the availability of genetically based tests to ascertain those at increased risk for cancer may have on the legal duties owed by physicians to patients. This new technology arguably elevates certain standards that are already in existence and creates some new ones.

When caring for a patient who may have a genetically based predisposition to cancer, the physician has an obligation to take a thorough family history. He or she also may have a new duty to inform the patient that information derived from predictive testing will be relevant to other family members and that it may generate a pressure to disclose private facts to relatives. There is, thus far, no directly relevant case law on this question. The best way to handle the issue is prospectively, that is to inform the individual prior to testing that genetic information may be of great importance to relatives. Perhaps genetic testing will someday become so important in medicine that we will alter our very definition of confidentiality to focus on the nuclear family rather than the individual.

Of interest, a recent report from the Institute of Medicine (1) supports a 1983 Presidential Commission Report (4) that suggested an exception to the principle of confidentiality when the caregiver has strong reason to believe that a second individual at risk is unlikely to become so informed from any other source and that lack of knowledge poses a serious threat to health or reproductive planning.

Growing concern that genetic information might be used improperly by insurers to deny coverage or to charge higher premiums to persons perceived to be undesirable clients because of increased reproductive risks or increased predisposition to disease (genetic discrimination) has led many geneticists and genetic counselors to warn their patients about this possibility (5). While there is no firm evidence to suggest that this has become a standard of care, it would not surprise me if professional groups advocated this practice.

The issue of who should have access to a person's genetic information raises complex questions that would benefit from social consensus and rule making. It may, for example, be appropriate to forbid life insurance companies from charging persons with moderately increased, genetically based risk for colon cancer higher premiums. On the other hand, it may also be appropriate to require applicants for jobs that directly affect public safety to make disclosures about predispositions they have for disorders that could compromise their abilities.

The Americans With Disabilities Act of 1990 does not explicitly state whether currently healthy persons who carry an allele that predisposes to disease meet its definition of a disability and, therefore, secure its protection. The reach of the law will be defined over the coming decade through judicial interpretation of the thousands of lawsuits that have been filed already.

The primary physician has a duty to refer the patient to an appropriate specialist if he or she is not adequately trained to counsel about the genetic risks, the test, or the consequences of a positive result. Physicians also have a duty to inform a patient if they have an atypical opinion about a particular test, such as favoring a test that most others no longer use. Not all of these

duties have been clearly articulated by the courts, but one may infer the likely outcome should they be litigated.

Predictive genetic testing raises novel issues about testing children. In the case of testing for Huntington's disease, a clinical consensus has developed not to offer tests to people under the age of 18 (6). This paternalistic stance is defensible because the disease usually manifests in mid-life, there is no known meliorative intervention, and knowledge of being a gene carrier can be emotionally devastating. Such an absolute rule is not, however, appropriate for disorders that have their onset before the age of 18 and for which there may be forms of surveillance or intervention that could confer clinical benefits. Pediatricians need to become involved in developing criteria by which we help parents judge when predictive testing is appropriate for a child. We should not assume that a parent's request is always in the best interests of the child (7).

Over the next few years, DNA banking may become a not uncommon activity in oncology. If it does, oncologists may need to inform patients that because DNA banking is not (yet) subjected to regulatory oversight, the security accorded to tissue or information in a bank may not be adequate. Physicians will not easily be able to advise patients about the quality of the repository, the degree to which it is able to protect the integrity of an immortalized cell line, or the privacy of genetic data.

Conclusion

In conclusion, the rapid expansion of DNA-based diagnostics, especially since these new tests confer the possibility of iden-

tifying persons at increased risks for diseases that can be averted, cured, or ameliorated through timely intervention, suggests that there will be great interest in their rapid introduction into clinical medicine. Oncologists, working through relevant professional groups, have an opportunity to help guide this transition in an orderly fashion. If they do not do so, it is likely that nonmedical groups, such as state departments of public health, may control this process. The least desirable (but all too common) outcome is that standards of practice will be driven in response to malpractice litigation.

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Genetic Testing for Cancer Predisposition: Behavioral Science Issues

*Caryn Lerman, Robert T. Croyle**

The discovery of major cancer susceptibility genes is likely to create strong pressures for clinical testing from biotechnology companies, insurance carriers, the medical community, and the public. However, before genetic testing for cancer predisposition is made widely available, we must identify the optimum strategies to enhance informed decision making, minimize adverse psychologic consequences, and promote adherence to recommended surveillance. This report provides an overview of behavioral research in these areas and, on the basis of this literature, presents suggestions for developing effective and ethical genetic testing protocols. [Monogr Natl Cancer Inst 17:63-66, 1995]

News of the discovery of major cancer genes is likely to generate strong pressures for clinical testing from biotechnology companies, employers, insurance carriers, the medical community, and the public (1,2). However, before such testing is made widely available, a variety of psychosocial and ethical questions must be addressed through careful research. This report will present data on the demand for genetic testing for cancer predisposition and will address two key research questions: 1) What are the optimum strategies to facilitate informed decision making for genetic testing for cancer predisposition? 2) What are the likely psychologic consequences of such genetic testing (3,4)?

Demand for Genetic Testing for Cancer Predisposition

Recent studies (2,5) suggest that the demand for genetic testing for cancer risk is likely to be very great, even among persons who are unlikely to have predisposing mutations. For example, we conducted telephone interviews with 121 unaffected first-degree relatives of patients with ovarian or breast cancer (2). Most of these women had only one relative affected with late-onset disease. Respondents were provided with a brief description of the BRCA1 gene, emphasizing that mutations of this gene account for fewer than 5% of all breast and ovarian cancer cases. Seventy-five percent of these unaffected women said that they "definitely would want to be tested" for BRCA1, and 20% said that they "probably would want to be tested." Personal belief about the likelihood of having an inherited BRCA1 mutation was the strongest determinant of interest in testing. Surprisingly, 59% of the women believed that they were somewhat or very likely to have an inherited mutation, despite the fact that very few of these women had any significant familial risk. Women

who were more anxious and worried about their risk expressed greater interest in BRCA1 testing compared with women who were less anxious. Similar results were obtained in a population-based study of interest in genetic testing for colon cancer predisposition (5).

It is possible that self-reported interest in genetic testing for cancer predisposition will not translate into actual use. Earlier studies of interest in genetic testing for Huntington's disease (HD) indicated that more than two-thirds of persons at risk were interested in testing. However, since the initiation of predictive testing for HD, fewer than 20% of persons at risk have come forward for testing (6,7). In the cancer domain, self-reported interest in genetic testing is more likely to translate into actual use, since there are good prospects for early detection and treatment of breast and colon cancers. And, even if the proportion of eligible participants is small, the total number of interested participants might overwhelm the genetic counseling resources currently available.

Informed Decision Making for Genetic Testing

The specific motivations for genetic testing reported by women in our study suggest that many of them lack understanding of the benefits and limitations of BRCA1 testing (2). Two of the most commonly stated motivations for genetic testing were to learn about one's children's risks and to be reassured. These results are similar to those from studies of predictive testing for HD (8). However, unlike HD, a negative BRCA1 result would not eliminate the possibility of breast or ovarian cancer developing in oneself or one's daughters. In fact, a negative BRCA1 result would not even imply a reduced risk, unless the individual was known to be a member of a BRCA1-linked family. Thus, for the majority of women with a family history of breast or ovarian cancer who do not have an altered BRCA1 gene, testing may not lead to reductions in anxiety or uncertainty. One would expect similar misconceptions to be prevalent among persons at risk for colon cancer; however, this has yet to be examined. If genetic testing proceeds without awareness of the uncertainties associated with risk figures from DNA testing, participants are more likely to experience

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See "Note" section following "References."

psychologic distress and may be less likely to adhere to recommended surveillance (3).

It is essential, therefore, that educational and counseling methods be developed to facilitate informed decision making among individuals who express interest in genetic testing for cancer risk. Research concerning physician-patient communication has shown repeatedly that patients fail to remember or comprehend much of what they are told (9). Ensuring comprehension of the complex nature of the inheritance of cancer will be a particular challenge for health educators. Research conducted in other genetic counseling contexts has demonstrated that genetic counseling can significantly improve the knowledge of some patients. Nevertheless, participants in genetic counseling continue to hold inaccurate beliefs regarding their level of risk (10).

With respect to genetic testing for cancer predisposition, potential participants must understand the possible benefits and limitations of genetic testing for someone at their current level of risk. Key facts about the limitations of genetic testing include the incomplete penetrance of cancer genes (all persons with inherited mutations do not develop cancer) and the etiologic heterogeneity of the cancer phenotype (cancer can arise in persons who do not have inherited mutations). Several potential risks of genetic testing must also be addressed during the informed consent encounter. One of these risks is the potential for adverse psychologic effects on the individual and his or her family members and the relationships between these individuals. Other potential risks include potential losses of insurance and employment and potential social stigmatization.

Studies (11) of the informed consent process have identified a variety of potential barriers to adequate informed consent that may operate in the genetic counseling context. These barriers include lack of formal education, cultural differences in the meaning of risk information, and cognitive biases in risk perception and decision making. For example, most individuals overestimate the likelihood of rare events (e.g., breast cancer before the age of 40 years), particularly if the event is very salient (e.g., intensive media coverage about breast cancer in younger women) (12). Another common bias is the tendency to choose an option that will completely eliminate a small-magnitude risk over an option that will reduce a large-magnitude risk to a low (non-zero) risk. These findings are consistent with research in genetic testing that has shown that most counselees have difficulty using probability information in the decision-making process (13,14). These biases have also been observed among women with a family history of breast or ovarian cancer, many of whom grossly overestimate their risk and expect that a negative BRCA1 result will eliminate completely the possibility of cancer development (2).

Emotional factors can also seriously compromise the informed consent process. This is one reason why the timing and rate of risk communication must be considered carefully (15). For example, stress and anxiety can interfere with comprehension of complex risk information, impair problem-solving ability, reduce recall of information, and lead to ill-considered decisions (16). In the genetic-testing domain, a study (17) of individuals at risk for HD found that high levels of perceived susceptibility and a lack of reassurance were associated with

difficulties in the genetic decision-making process. The potential for emotional factors to interfere with informed consent is particularly relevant to persons at increased risk for cancer because of their high levels of perceived risk and cancer anxiety (18).

The potential effect of emotional factors on comprehension of cancer risk information is supported by preliminary data from our ongoing randomized trial (CA57767). This project is evaluating the impact of individualized breast cancer risk counseling among women with a family history of breast cancer. Among women who received individualized breast cancer risk counseling, those with high base-line levels of breast cancer anxiety were significantly less likely to show improvements in their risk comprehension following the counseling session (Fig. 1).

These data suggest that information alone may not be sufficient to ensure adequate comprehension and informed consent for genetic testing for cancer predisposition. For some individuals, additional pretest counseling will be required to address emotional responses that may impair decision making about genetic testing. Such counseling should address the psychosocial impact of cancer in the family, the anticipated impact of alternate testing decisions and results, personal coping skills, and plans for communicating test results and obtaining support (3,19,20). Research is urgently needed to evaluate alternate models for providing pretest education and counseling for genetic testing for cancer.

Psychologic Consequences of Genetic Testing for Cancer Risk

Another key question concerns the potential psychologic sequelae of cancer risk notification among persons who elect to receive genetic test results (19-21). A prospective study (22) of the impact of predictive testing for HD suggests that, for most participants, any adverse effects of risk notification may not be

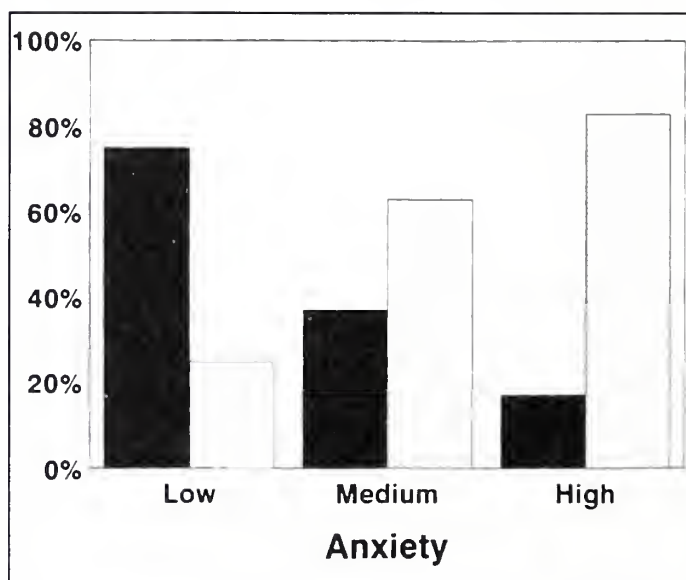


Fig. 1. Proportion of subjects with improvements in risk comprehension by pre-counseling anxiety level. ■ = improved; □ = not improved.

serious or long-lasting. Participants in a pilot-predictive testing program were administered a battery of psychologic measures before testing and at multiple follow-up points. At first follow-up (7-10 days after testing), there were significant differences on all measures between persons identified as carriers and non-carriers of the HD gene. However, by 12 months there were no significant differences. This model could be adapted easily to evaluate the psychosocial and medical impact of genetic testing for major cancer susceptibility genes, such as BRCA1 and MSH2.

Any extrapolation from preliminary evaluations of HD testing must be made with great caution, however. The low rate of use seen in the HD studies means that study participants tend to be highly self-selected. A survey by Quaid (23) indicated that most testing centers in the United States were not collecting any outcome data. Furthermore, "the centers reporting outcome data are those centers with the most experience offering predictive testing and those which most closely follow recommended protocols" (23). Given the vastly greater potential demand for cancer-related predictive testing, early evaluations conducted within carefully controlled research protocols may underestimate the risks of testing in settings where psychosocial support and follow-up are minimal or nonexistent.

Another important objective of research on the effects of genetic testing for cancer should be to identify factors that influence individuals' responses to cancer risk information. Potential effect modifiers include age, sex, education, expectations, coping styles, psychologic morbidity, and social support. In a study (24) of predictive testing for HD, the impact of base-line levels of psychologic morbidity was shown. In this sample, the likelihood of adverse effects following notification of HD risk status was significantly greater for persons who were more distressed before receiving their results. As applied to cancer, this line of research could help to identify persons most vulnerable to adverse psychologic consequences of risk notification and would provide information useful for allocating scarce resources for additional psychologic counseling.

Adjunctive psychologic counseling after receipt of genetic test results potentially can minimize any adverse effects of risk notification (3,20). The provision of such support, either personally or through referral, is a duty of clinical geneticists and genetic counselors (25). Reports from predictive testing programs for HD suggest that such counseling will be important for persons identified as being at increased risk, those at decreased risk, and those who decline testing (22). In the cancer domain, post-test counseling could include discussion of plans for communicating test results, instruction in coping strategies, discussion of options for prevention, and recommendations for surveillance (3). In addition, it must be recognized that genetic information has implications, not only for the individual who undergoes testing, but also for their partners, children, siblings, and parents (26). As such, follow-up support should be extended to family members as well.

By minimizing the adverse psychologic sequelae of genetic testing for cancer predisposition, counselors are likely to enhance the likelihood that individuals will adhere to recommended surveillance. Previous studies (27,28) have shown that psychologic distress can deter adherence to breast self examina-

tion, clinical breast examination, and mammography among women with a family history of breast cancer. This effect may be especially pronounced for high-risk individuals who have less formal education (28). Thus, without appropriate education and psychosocial counseling, the potential for genetic testing to reduce cancer mortality may go unrealized.

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Note

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Gene Tests and Counseling for Colorectal Cancer Risk: Lessons From Familial Polyposis

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Familial adenomatous polyposis (FAP) is a well-defined, inherited colorectal cancer syndrome due to mutations in the APC gene. Genetic counseling and predictive gene tests for FAP will likely be incorporated as a first step in risk assessment for this condition. Our experience with predictive gene testing for FAP sheds important light on the impact of such tests for families at risk for FAP or colorectal cancer. We counseled and tested 47 adults and 36 minors at risk for FAP. Gene test results changed the risk of FAP for a given individual from a priori 50% to essentially zero or 100%. These individuals and their family members were interviewed before and after disclosures of APC gene test results to examine issues related to patients' knowledge about FAP, risk perception, reasons for seeking gene testing, and anticipated meaning of the results. We found that the gene test is imbued with meaning beyond determination of gene status in families who choose gene testing. The at-risk patient has preformed, well-entrenched conceptions of what having FAP or colorectal cancer entails, and family relationships and identity may be strongly linked with disease or gene status. We have found that genetic testing of minors requires additional counseling considerations and effort to ensure their understanding of FAP and the gene test. Importantly, their understanding of the clinical and social meaning of the gene test result must be elicited. For all patients, the value of counseling includes reduction of uncertainty and adjustment of misperceptions. Genetic counseling guidelines for this emerging clinical service are presented. [Monogr Natl Cancer Inst 17:67-71, 1995]

During the past several years, there has been a considerable increase in our understanding of the genetic and molecular bases of colorectal cancers, especially hereditary forms (1-8). This rapidly developing knowledge will lead to an improvement in the clinical management of risk assessment. In particular, we are now able to offer gene tests to individuals at risk for familial adenomatous polyposis (FAP). The new technology carries a responsibility for the clinician to help the tested individuals understand the implications of the gene test.

The purpose of our study was to characterize the context of gene tests from the patients' perspective in order to develop rational guidelines for genetic counseling and predictive testing for risk.

FAP is a well-characterized, inherited colorectal cancer syndrome with high (>90%) penetrance (9-11). Other appellations of the clinical entity include familial polyposis coli, adeno-

matous polyposis coli, or Gardner's syndrome. The U.S. incidence of FAP has been estimated to be approximately 1/8000 to 1/10 000. The hallmark of this condition is the presence of multiple (>100) adenomatous polyps in the colon and rectum. The average age at onset of the colon adenomas is around 15 years. When the adenomatous polyps appear, the risk of colon cancer in untreated persons is essentially 100%, usually by the fourth decade of life. Variant features, in addition to the colonic polyps, may include polyps in the upper gastrointestinal tract, extraintestinal manifestations such as osteomas and epidermoid cysts, desmoid formation, congenital hypertrophy of retinal pigment epithelium, and malignancies, such as thyroid tumors. Interestingly, a large proportion (as much as one third) of newly diagnosed patients with FAP are "spontaneous mutations," being the first person in the kindred to present with colonic polyposis.

FAP is an autosomal dominant disease, and offspring of affected individuals are at 50% risk of inheriting the disease. Conventional management of individuals at risk for FAP has consisted of colon screening by endoscopy beginning around puberty. Annual screening is performed until adenomas are detected. Prophylactic colectomy is indicated when polyps are too numerous to be removed by endoscopy (12,13) and enables the patient to have subsequent normal life expectancy. Follow-up surveillance by endoscopy for upper gastrointestinal neoplasms is recommended for persons with the diagnosis of FAP. Increasingly, management of FAP will incorporate genetic testing of at-risk individuals as a prelude to the colon-screening regimen (14), as the use of gene tests will change the screening course for those individuals who do *not* have the gene.

Methods

This research study was approved by our institutional review board. We identified individuals at risk for FAP through our hereditary colorectal cancer family registry. At-risk individuals aged 5 years and older were eligible if they were asymptomatic, had a parent who had a known diagnosis of FAP, and the APC

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See "Notes" section following "References."

gene mutation in the kindred was identified and detectable by our gene tests. We identified and offered gene tests to 57 adults and 38 minors. Ten adults and two minors declined to be tested. Our study is based on gene tests performed on 47 adults and 36 minors at risk for FAP.

Predictive genetic testing was done by direct detection (15) using peripheral lymphocyte DNA. More recently, a simpler test has been reported, which assays for the truncated protein product using *in vitro* transcription of the APC gene or allele-specific expression to identify promoter or splice mutations by reduced levels of APC transcripts (16). This latter technique considerably enhances the availability of testing to at-risk individuals.

Gene test results changed risks for FAP from a priori 50% to essentially zero or 100%. We modified recommended follow-up screening based on gene test outcomes (17). Briefly, when the test is APC gene positive, no change in conventional screening guidelines for colon polyps was recommended; that is, these individuals should have annual colon examinations with flexible sigmoidoscopy beginning around age 10 or 11 years, along with counseling to prepare for an eventual prophylactic colectomy, and genetic counseling about the risk of FAP for future offspring. Persons who are gene positive also will need follow-up surveillance for extracolonic tumors. For the majority of persons who are APC gene positive, it is very likely that colon adenomas will develop. However, it is *not* indicated to surgically remove polyp-free colons even in individuals who are gene positive. Timing of surgery should depend on the number of polyps found in the colon. When the gene test result is APC gene negative, colon screening can be substantially reduced, to three or fewer time points, at ages 18, 25, and 35 years, with the option of repeating the gene test at any time to confirm the initial finding. The individual's lifetime risk for colorectal cancer is the general population risk of approximately 5%, and colon cancer screening would resume again around age 50 years, according to conventional guidelines. These individuals can be assured that their offspring will not be at risk for FAP.

Enrolled individuals and their family members were interviewed by telephone before and after disclosures of APC gene test results. All interviews were conducted by one person (P. A. Boyd) using open-ended questions that addressed a set of preidentified research topics but also included those initiated by the participants. All interviews were tape-recorded with interviewees' consent and transcribed. Interviews were analyzed for issues related to knowledge about FAP, risk perception, reasons for choosing gene testing, and anticipated meaning of the results.

Genetic Counseling Results

We have found that genetic testing for FAP should always include a minimum of two face-to-face education-counseling sessions, one to fully explain the test and discuss its potential implications for the patient (preparatory session) and another to disclose test results to the patient (disclosure session). For all gene-positive patients, we strongly recommend a third session (follow-up session), conducted either by telephone or in person, in which 1) the patient is allowed a second opportunity, free from the initial emotional reaction to the test result, to ask ques-

tions about clinical management and 2) the clinician can determine if referral to a mental health professional for additional support is indicated. On the basis of our experience, we believe that each of the elements described below constitutes the minimal requirement for appropriate education and counseling.

Preparatory Session

The goal of the preparatory session is to ensure that the patient is adequately equipped to make a fully considered, independent decision to undergo genetic testing and is well prepared to receive the results. The session should focus on providing patient education and achieving an understanding of the perspective that the patient brings to genetic testing. With genetic diseases such as FAP, at-risk patients typically have a preformed, well-entrenched conception of what having the disease entails because of their extensive first-hand, often multigenerational, experience with affected relatives. Moreover, family relationships can be profoundly marked by issues such as guilt and blame, and personal and familial identity may be strongly linked with FAP status. Thus, genetic testing is imbued with meaning for certain patients much beyond its ostensible function as a simple determiner of genetic status. Understanding of the patient's perspective is an integral feature of the counseling inasmuch as issues requiring special attention can be identified and the patient's pre-existing social context can be taken into account in assisting her/him to adjust to genetic test results. In addition, it aids in the clinician's ability to devise a mutually agreeable treatment plan that has a fair chance of acceptance by the patient who tests gene positive.

These two components of the preparatory session should specifically include the following:

- 1) Educating the patient about (a) genetic testing's purpose, (b) treatment implications of gene-positive and gene-negative results, (c) FAP risk of patient's offspring given a gene-positive or gene-negative result, and (d) potential consequences of knowing one's genetic status (Table 1). The test's purpose, risks, and treatment implications based on genetic status have been described above. Patients should be apprised of the potential consequences of knowing one's genetic status. Concentration on the patient's perspective should begin with exploring the patient's understanding of FAP and to offer, if needed, a reframing that is consistent with current clinical understanding of the natural history of FAP, its treatment, and prognosis. Such discussion can be considerably reassuring to those who have seen multiple deaths and/or cases of cancer within their family, which are often primarily due to late diagnosis. Conversely, however, it is important also to recognize that new, potentially unsettling information may be brought to light about which the patient was previously unaware.

- 2) Understanding the patient's perspective in terms of (a) FAP's features and its management including family-specific experiences, (b) personal risk perceptions, (c) reasons for choosing genetic testing, and (d) anticipated meaning of gene-positive or gene-negative result for the patient and her/his family. Counseling should elicit the patient's perceptions of personal FAP risk in terms of knowing not only the objective risk but also, even more importantly, his/her "gut feelings" about this risk. We found that almost all persons were aware that their risk was

Table 1. Potential consequences (positive and negative) to patients of APC gene tests

Gene status	Consequences
If gene positive	Positive <ul style="list-style-type: none"> • Reduction of uncertainty • Able to plan for future health care needs, finances, career • Able to make informed childbearing decisions
	Negative <ul style="list-style-type: none"> • Dashing of hope to escape FAP • Anger at one's circumstances or toward affected parent • Feeling different or stigmatized, alienated from others • Temporary or chronic depression and/or anxiety • Potential loss of insurability • Guilt regarding children's FAP risk • Jealousy toward gene-negative siblings
If gene negative	Positive <ul style="list-style-type: none"> • Relief • Guilt-free childbearing • Better potential for insurability
	Negative <ul style="list-style-type: none"> • "Survivor guilt" (feeling guilty for not having it when other relatives do)

50%. Upon further discussion, however, they invariably offered descriptions of factors that they suspected altered this risk. These factors included the presence of certain phenotypic markers such as epidermoid cysts; similarities to affected family members such as gender, bowel patterns, and personality; and miscellaneous factors such as being first-born or having a weakened physical constitution.

Discussing the patient's risk perceptions thus allows the clinician to foresee problems when prior beliefs are considerably at odds with determined genetic status. Obviously, it should be expected that those who are gene positive and feel prior to testing that their risk is minimal might require additional support in adjusting to knowledge of their genetic status.

Discussion of a patient's reasons for seeking genetic testing and anticipated meaning of a gene-negative or gene-positive result can serve to unearth understanding of genetic testing and treatment implications as well as to illuminate some of the less visible, yet profound, effects precipitated by the testing. In our experience, simply asking the following three questions has been invaluable in this regard:

1) Why did you decide to undergo genetic testing for FAP at this time? 2) What do you think it will mean for you and your family if you have the FAP gene? 3) What do you think it will mean for you and your family if you don't have the FAP gene?

Importantly, the potential for misuse of genetic testing in guiding treatment has become evident in answers to these questions. For example, among some parents whose children have been tested, we have witnessed an earlier-the-better philosophy regarding colectomy. These parents believe that the sooner the colon is removed, the better off or more well protected from cancer the child will be. Emphatically, colectomy timing should not be based on genetic status. As before the availability of genetic testing, colectomy is indicated only by the number and condition of colonic polyps.

Disclosure Session

Disclosure of test results should be scheduled in the best interest of the patient such that it does not occur in the midst of other stress-producing circumstances that can exacerbate response to test results. This may mean that some patients will elect to receive their results at a date farther in the future when they feel better equipped to handle the outcome. It should be recognized also that other patients may have a change of heart and choose not to receive the results at all. Even if the patient is found to be gene positive, the clinician has an ethical obligation to accede to a patient's wish not to know the results.

A discussion of treatment recommendations that should have been provided in the preparatory session should be reiterated after disclosing the patient's results. However, from our experience, some patients recall little (other than their results), having difficulty attending to the discussion once they learn of their genetic status. In these cases, patients seemed to be overwhelmed by their own emotional reaction that, for some, was surprising. Consequently, subsequent to the disclosure session, the patient should be sent a detailed follow-up letter that carefully reiterates the following: 1) the genetic test result and what it means for current and future health; 2) clinical management recommendations (e.g., colon-screening regimen); 3) FAP risk of the patient's offspring; 4) referral to a mental health professional (if this was discussed in the disclosure session); and 5) encouragement to schedule a follow-up session if more information and/or support is desired.

Follow-up Session

A follow-up session for gene-positive individuals should be offered as an option. This allows patients the time to consider their genetic test results and to formulate important questions that might not have occurred to them during the disclosure session. Follow-up also allows the clinician to observe the patient's adjustment to the result and to offer a referral for counseling if indicated or requested by the patient. It is useful if the clinician informs any referral counselors about genetic testing for FAP so that they have some understanding of the issues involved before seeing the patient. Finally, the follow-up session is a useful occasion to set up a colon-screening schedule.

Special Issues in Testing Children

There has been recent debate on the appropriateness of genetic testing of minors (18,19), particularly for conditions that have onset later in adulthood or for which there is no intervention to change the outcome. In the case of FAP, gene testing for risk is relevant, as the first onset of colonic lesions and medical management normally occur in childhood. On the basis of our experiences thus far, we have identified several counseling issues bearing on the genetic testing of children. First, it is important to involve children in the preparatory session so that they clearly understand the purpose and implications of the testing. Understanding of the testing necessarily involves awareness of FAP, and an essential task should be to determine if there are any psychologically damaging misperceptions held by the child regarding what having FAP and genetic testing itself means. We

find that parents are not an accurate gauge by which to judge a child's understanding, inasmuch as they commonly overestimate or underestimate their child's knowledge of FAP. In some families, children were told by their parents about FAP many years before with no subsequent reiteration; in other families, parents withheld details as a protective maneuver. In the absence of discussion and in the face of concrete examples of what having FAP means, children develop their own constructions of the disease that may be unnecessarily frightening.

It is important, therefore, to address the child directly to determine FAP-related knowledge and conceptions and to ask if the child has any questions about the genetic testing. Care must be taken to avoid offering too much information because children often have an awareness threshold that, if surpassed, may result in unneeded, undesirable anxiety. Also, content to be discussed should be checked out with parents prior to initiation of any conversation with the child. In some cases, respectful negotiation with parents who wish to withhold information from children may be required. We have found that most parents do want their children to be informed and will often welcome the clinician's help in this regard.

In families where affected parents had already had FAP-related surgery, children were very aware of this feature of the disease. Thus, they typically focused on the genetic test result as the factor that would determine whether they too would need surgery or, in those cases where parents had been visibly ill, whether they would suffer the same fate. Because of the pervasiveness of this focus on surgery, particularly among younger children, we recommend that several reassurances be offered as a general practice. For the child, these include the following:

- Help is available if you have the FAP gene (e.g., the doctor can keep a check on your colon to make sure you don't get sick/develop cancer).
- If you need surgery, it is not likely to happen for many years.
- The type of surgery you will probably have won't result in a permanent ileostomy and will allow you to have bowel movements similar to those of other people.
- If you ever need surgery, you will be asleep while it is going on.

The disclosure session should be arranged so that parents have an opportunity to deal with their feelings and gain control before facing the child with the results. Many parents who felt well prepared prior to the disclosure session reported feeling "shocked" or "devastated" upon learning of their child's genetic status, particularly when the number of children (often parents want all children tested at once) and/or which child was found to be gene positive differed from their prior expectations. The parents may be feeling anticipatory grief that the child's life will not be free from dealing with FAP and become sad for that reason rather than because of a feeling that life with FAP is so objectionable. In fact, most parents with FAP describe themselves as "normal" and indicate that there are worse fates than having FAP.

As a result of our observations, therefore, we do not recommend telling both children and their parents the results at the

same time. A delay, if even for only a few minutes, that allows parents time to compose themselves is requisite so that they can avoid alarming the child unnecessarily. It is likely that some parents will even prefer to tell the child themselves at home, and the clinician should be prepared to offer advice on how to do so. Parents should be cautioned that a delay in disclosing results to children when the children know parents are in possession of the information can be devastating to children. If a delay is anticipated, parents should be advised not to let the child know that they have the results until such time as they are ready to reveal them.

Timing of genetic testing and disclosure of results should be thoroughly discussed with parents. Many parents do not anticipate the stress that genetic testing adds to the child's and their own life. Thus, it is advisable to schedule genetic testing so that it does not coincide with other stress-producing events.

Finally, many gene-positive children have expressed concern about how they will be perceived by friends and peers. Thus, we strongly recommend that the disclosure session include discussion about the advisability of telling the results to others, as well as strategies for relaying the information if the child elects to do so. Thus far, those who have told others have not experienced any adverse reactions. Initial feelings of being different from others quickly dissipated when friends and peers did not treat them differently than before and in fact expressed interest in the genetic testing. However, children's stories about disclosing their genetic test results to friends reveal that the concepts of genes and polyps are difficult to convey. As a result, in one case, a 9-year-old girl told friends that she had "cancer" because this was something they all understood. Thus, helping the gene-positive child to formulate an explanation to give to others that leaves self-esteem undamaged is one of the most valuable contributions a clinician can make to the child's adjustment to her/his genetic status.

In summary, predictive gene tests for FAP, and eventually colorectal cancer susceptibility, will become widely available. Our analysis of this sample of at-risk adults and children represents a first attempt to identify how the social context shapes their knowledge, risk perception, and meaning of the gene test. We conclude that genetic counseling is an important component to add to the array of changes in the management of individuals at risk for FAP. Careful consideration and thorough discussion of the implications of the test both before and after the results are disclosed are of great importance.

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Notes

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Psychological Counseling Strategies for Women at Risk of Breast Cancer

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Women with family histories of breast cancer have a much higher risk of developing the disease than women in the general population. In the absence of primary prevention for breast cancer, secondary prevention in the form of early detection is our best bet against premature morbidity and mortality. This article describes the most salient psychological issues for high-risk women as well as ways for improving screening behaviors. Based on our work and other studies in the literature, we found that there were several key variables related to psychological distress and surveillance behaviors. Barriers to screening were a major reason why women did not engage in any breast cancer prevention behaviors. Cognitive deficits, in terms of lack of knowledge, and breast cancer misbeliefs contributed to poor adherence to screening. Most important, anxiety or emotional distress not only interfered with adherence to screening but also affected quality of life negatively in that many women needed psychological counseling. In developing psychological counseling strategies for high-risk women, we focused on the treatment outcomes of reducing emotional distress, decreasing perceived vulnerability, and improving adherence to screening behaviors. We conducted a preliminary study by piloting a group psychoeducational intervention for 6 consecutive weeks. This intervention was found to significantly reduce perception of risk ($P < .02$) and to increase adherence to screening behaviors ($P < .01$). If proven effective in a randomized controlled trial, this intervention can be proposed to other cancer centers and prevention programs for implementation and enhancement of the behaviors among high-risk women that will assure early detection and decrease breast cancer mortality. [Monogr Natl Cancer Inst 17:73-79, 1995]

It is estimated that one of every eight women will develop breast cancer during her lifetime (1). The risk is not evenly distributed in the population and is two to three times higher in women who have a first-degree relative with breast cancer as compared with women who have a negative family history (2,3). There is also some evidence that for women with a first-degree relative with bilateral premenopausal breast cancer (2,4) or unilateral breast cancer under the age of 40 years (5,6), the risk is even greater.

Women at increased risk of breast cancer need modifications to their screening guidelines (7). One suggestion is that women

with a first-degree relative with premenopausal breast cancer should have mammograms and clinical breast examinations (CBEs) at an earlier age (e.g., aged 35 years) (8). There is a consensus among those in charge of high-risk surveillance programs in the United States (e.g., Memorial Sloan-Kettering Cancer Center and the Strang Cancer Prevention Center, New York, N.Y., The Johns Hopkins Oncology Center, Baltimore, Md., and the University of California at Los Angeles Breast Center, Calif.) that women with strong family histories of breast cancer have mammograms every year after the age of 40 years and CBEs every 4-6 months (9). While there is no primary prevention for breast cancer, secondary prevention in the form of early detection offers the best chance against premature mortality.

In this article, we identify who is at high risk for breast cancer because of genetic factors. The levels of psychological distress and important barriers to screening in these women are recounted. Most important, counseling strategies to ameliorate the negative psychological sequelae and to improve adherence to screening recommendations are described.

Definition of High Risk

Despite the evidence linking genes (BRCA1, in particular) with breast cancer, reliable risk information has not been provided to the target population, that is, those at increased breast cancer risk conferred by family histories. The primary consequence has been a failure to provide information regarding appropriate surveillance actions to meet the added risk (9). This gap in the information chain assumes even more importance with gene testing for cancer predisposition, which is now on the verge of clinical application. A knowledge of risk-assessment principles and tools is essential to enable identification of candidates appropriate for testing and to provide those at risk with realistic risk figures for decision making.

In the absence of gene testing for breast cancer in the clinical setting, there needs to be a method of identifying women who are most likely to be at increased genetic risk. Two recent risk

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See "Notes" section following "References."

assessment systems derived by Gail et al. (10) and Claus et al. (11-13), have been accepted in establishing breast cancer risk. They differ from earlier systems because they are models based on large datasets rather than empiric analyses. The Gail model factors in epidemiologic risks (age at menarche, parity, and number of biopsies) and family history to arrive at relative and absolute risks based on the age of the consultand. It tends to underestimate risk due to family history because it only counts two first-degree relatives and does not recognize affected second-degree relatives as contributing to risk; affected paternal-line family members are also ignored. The Claus model is based solely on family history and age(s) at diagnosis of affected relative(s), with cumulative risks calculated for up to two affected relatives (first and/or second degree). The model assumes the existence of a rare dominant allele responsible for breast cancer predisposition. Neither the Gail nor the Claus model provides a fit for every positive history. The Gail model is useful when family history is not striking and other risk factors are present. Its most notable application has been in determining eligibility for the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, in which 16 000 North American women have enrolled. This is a double-blind randomized study of the effectiveness of tamoxifen versus placebo in preventing breast cancer.

We used the Claus model for defining risk status and entry eligibility for the Strang Breast Surveillance Program. Women had to fall into one of four high-risk categories: 1) two or more first-degree relatives (mother, sister, and daughter) with breast cancer before the age of 60 years; 2) a first-degree relative with bilateral premenopausal breast cancer; 3) a mother and maternal grandmother with breast cancer before the age of 60 years; or 4) a first-degree relative with unilateral breast cancer before the age of 40 years. These criteria were selected to include women whose lifetime risk of developing breast cancer on the basis of their family histories was between 17% and 50% (13). For example, a 30-year-old woman whose 27-year-old sister, mother, and maternal grandmother (both she and her twin sister had bilateral breast cancer before age 50) as well as six other second-degree relatives were all affected with breast cancer may be the carrier of an autosomal dominant gene (Fig. 1).

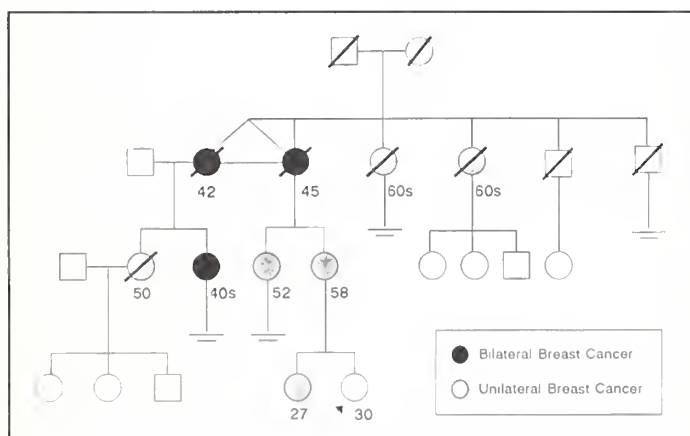


Fig. 1. Pedigree of a 30-year-old woman who sought risk counseling and screening recommendations.

Psychological Issues in High-Risk Women

Women who are at risk of developing breast cancer because of their strong family histories are also at higher risk for psychological distress (14-16). There are many issues for high-risk women who live with fear, anxiety, and uncertainty every day of their lives. The first and most overwhelming issue for women is their anxiety about developing breast cancer. Anxiety peaks at certain points in their lives, for example, when a woman reaches the age her mother or sister developed breast cancer. At that age, a woman becomes concerned that she too will develop breast cancer and die of the disease. Another peak in anxiety occurs when a woman has the same number of children as her mother did when she developed breast cancer. Some women magically believe that if they have fewer children, they will be protected against breast cancer.

A woman's sense of vulnerability leads to an overestimation of risk that in turn heightens her subjective certainty of developing breast cancer. Data from other studies (17,18) indicate that a substantial number of women with a family history of breast cancer have a heightened perception of risk. In particular, the study done in the United Kingdom, where one of 12 women is at risk, found that more than 45% overestimated their risk for breast cancer and only 11% correctly identified their risk. More than 80% of the 503 women in our study overestimated their risk of developing breast cancer, some by as much as four times greater than their actual risk. Fifteen percent of the women in our study provided an accurate perception of their risk and 5% underestimated their risk. Underestimation most frequently occurred when a woman had a very high risk (35%-50%) and had not received risk counseling. Frequently, women report that they are "100% sure" that they will get breast cancer, as well as describing themselves as "walking time bombs." In other words, women at genetic risk do not wonder *if* they will get breast cancer but rather *when* it will appear.

The fear of disfigurement or death is a common theme and is sometimes worse for women who were young when their grandmothers, mothers, and sisters developed the disease and died. Fears, such as having mutilating surgery for breast cancer, which may be irrational, are prevalent in their thinking. Many women remember the radical Halstead mastectomies of 20 years ago and believe this type of surgery will be performed on them if they develop breast cancer.

Variations in guilt are pervasive in women at high risk. Some women feel guilty because they were not there either physically or emotionally for their relatives who had had breast cancer. Other women feel guilty because they may have passed a gene to their daughters. Many women feel guilty because they are so worried and concerned about breast cancer and yet they are healthy. Women who have not developed breast cancer while other relatives have the disease feel "survivor" guilt.

The misconceptions and myths about breast cancer are overwhelming for many women. Some of these have been passed from one generation to the next. One myth is, "If you get hit in the breast, you will develop breast cancer." A misconception about breast cancer is, "If you have fibrocystic breasts, this leads to breast cancer." Yet another misconception is, "If you have surgery for breast cancer, it spreads."

Frequently, women who have strong family histories of breast cancer feel powerless about the disease. Women think they have a gene, they cannot control it, and breast cancer is their destiny. In addition, they felt helpless when their mothers and sisters had breast cancer and feel hopeless about avoiding the disease themselves. In other words, a woman's sense of self-efficacy regarding the prevention of breast cancer is lacking.

Another psychological issue for women at high risk is their passivity and their use of denial regarding breast cancer and, in particular, adherence to screening. Women frequently make statements, such as, "If I don't think about breast cancer, I can't get it" or "I just don't want to know if I have breast cancer." Sometimes, women join a surveillance program and after having a couple of negative mammograms and CBEs, they feel protected and postpone their future screening dates.

Finally, one of the major issues surrounding all of the above concerns is that women feel isolated and alone. Women stated that their surviving relatives are reluctant to discuss breast cancer with them. Generally, these women feel that no one else knows how they are feeling. Their friends are not interested in discussing their "obsession" with breast cancer.

Studies have found that levels of psychological distress, such as greater cancer anxiety (14), more intrusive thoughts (15), and higher perceived susceptibility (16), were associated with a decrease in mammograms, CBEs, and breast self-examinations (BSEs). In our study, we found that levels of psychological distress, as measured by the Global Severity Index of the Brief Symptom Inventory (19), in high-risk women were one half to one standard deviation above the mean for normal women in the population. More than 28% of high-risk women were defined as having a level of psychological distress consistent with the need for counseling. One of our most striking findings was that high-risk women's scores were similar to those of women who were survivors of Hodgkin's disease and leukemia (Fig. 2). These high levels of distress diminished their quality of life. Many

women thought about breast cancer every day of their lives, postponed marriage, and decided not to have children because they were 100% certain they would develop breast cancer and die of the disease.

Screening Adherence

In our study of 503 women at high risk attending a surveillance program, we found lower rates of screening adherence in women who were more distressed. While 52% came in for regular CBEs, only 27% performed BSEs monthly. In women over the age of 40 years, less than one half (46%) came in for yearly mammograms. For all three methods of early detection, greater cancer anxiety and psychological distress were significant predictors of poor adherence. We also found that younger, well-educated women were less likely to perform a monthly BSE ($P<.01$). A multiple regression analysis revealed that women with the highest psychological distress levels had more barriers to screening as well as an interaction effect of low social support and more barriers (Table 1).

Barriers to Screening

Studies (20) have found that the major barriers to mammography are lack of physician recommendation or referral and the cost of having one. However, women who participate in the Strang Breast Surveillance Program are physician or self-referred and mammograms and CBEs are done at a low cost to the patient. While these major barriers have been eliminated for women in the Surveillance Program, other barriers impact on women having mammograms and CBEs and performing monthly BSEs.

Overestimation of risk is a major barrier to screening. The higher a woman's perception of risk, the less she adheres to regular mammograms and CBEs and the less she performs monthly BSEs. Often, the fear of finding a lump represents a

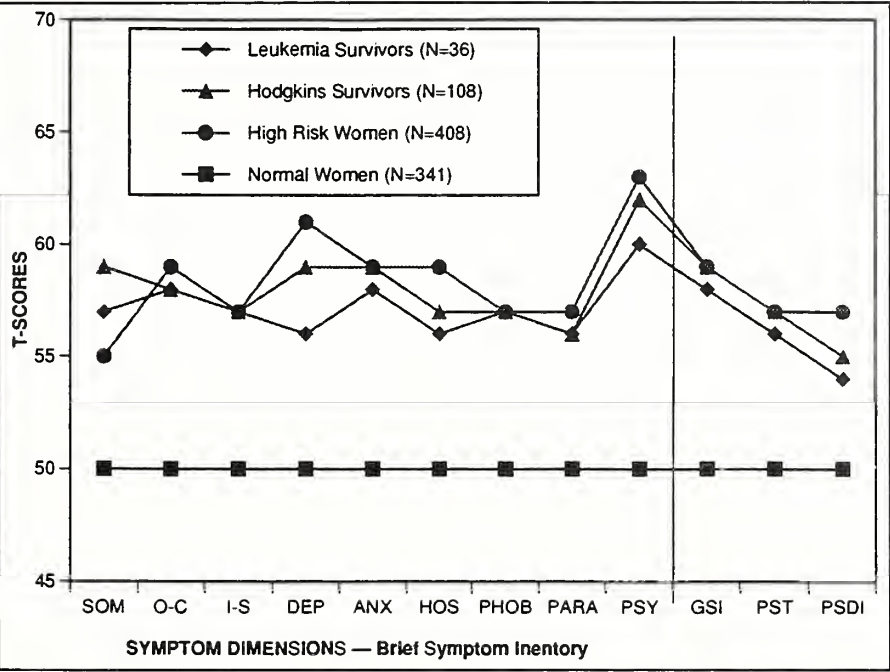


Fig. 2. Psychological distress scores of normal and high-risk women as compared with women who had Hodgkin's disease and leukemia. SOM = somatization; O-C = obsessive-compulsive; I-S = interpersonal sensitivity; DEP = depression; ANX = anxiety; HOS = hostility; PHOB = phobic anxiety; PARA = paranoid ideation; PSY = psychoticism; GSI = Global Severity Index; PST = positive symptom total; PSDI = positive symptom distress index.

Table 1. Factors predicting psychological distress (n = 420)

	Beta*	P
Perceived barriers	.83	.0001
Barriers and social support (low social support and many barriers)	-.72	.0001
Social desirability (denial of undesirable qualities)	-.31	.0019
Perceived risk	.12	.0288

*Multiple R = .68.

barrier. As the time gets closer for a woman to have a mammogram or CBE or perform BSE, her anxiety about what might be found increases. The intense fear associated with losing a breast through a mastectomy results in women postponing their appointments for screening. Frequently, women will avoid screening as a way of handling their fears.

Sometimes women are concerned about the levels of radiation they are exposed to during a mammogram. One woman believed that one more mammogram view would be her downfall and she would get breast cancer from it. Another barrier to screening adherence is the amount of physical discomfort from having a mammogram. Most women describe having a mammogram as uncomfortable. However, some report that it is extremely painful and this deters them from obtaining future mammograms.

In some families, cancer was a taboo subject (since it was frequently equated with a death sentence) and breast cancer was a secret for many years. Female sexuality is frequently associated with breasts by both men and women. Consequently, some women regard their breasts as desirable for intimate pleasure. This results in women feeling embarrassed about having their breasts examined by a physician or nurse practitioner or embarrassed about examining their own breasts.

Over one third of the women in our program report that coming to the clinic for an examination, whether it is a mammogram or CBE, is emotionally distressing. A clinic visit is a reminder of experiences with relatives and friends with breast cancer and evokes a multitude of responses in women. Some women become tearful when they walk in the door and others avoid screening as a way of circumventing the emotional upheaval. Taking time from other activities was also a barrier to screening for more than 50% of the women. It is evident that some women prefer doing anything rather than adhering to screening recommendations.

Improving Surveillance Behaviors

From the data above, it became clear that we had to find ways to ameliorate the negative psychological sequelae and to help women at high risk of breast cancer adhere to all three methods of screening. For most of the population, the cost of mammograms and physician recommendations are extremely important. Low cost, good-quality mammography clinics should be established for those who cannot afford the high cost privately. Also, perhaps the physician should make a mammogram appointment for women, rather than leaving it up to their discretion.

One way to improve screening adherence is to enhance the role of professionals. Physicians need to refer their patients for breast cancer screening on a timely basis. Primary-care clinicians should be developing protocols for risk assessment and work within the context of breast surveillance programs. One component of the assessment would be the genetic-risk assessment done by the genetic counselor or a health professional trained in this field. The manner in which risk information is provided to high-risk women is a crucial variable in the psychological distress and screening adherence equation. For example, if a woman has a 40% lifetime risk of developing breast cancer, this information can be presented to her by conveying the message that her chance of not developing breast cancer is 60%. Also, the risk counselor should advise her regarding the risk for 10-year intervals, as well as how much risk has already been expended during her life (10,21). This positive communication, coupled with screening recommendations tailored specifically to the woman, may help to provide reassurance regarding a longer life span and may reduce emotional distress.

Since barriers to screening resulted in psychological distress and decreased adherence, ways to diminish the barriers that interfere most with screening behaviors must be identified. Another method of increasing surveillance behaviors is to expand women's knowledge about early detection and breast cancer. Many women still equate breast cancer with death, and they lack state-of-the-art information regarding low-dose radiation from mammography, breast-conserving surgery, and a 92% cure rate with the early detection of breast cancer.

Another aspect of improving screening adherence revolves around reinforcement and reminders of specific behaviors. Women need to be taught how to do a BSE properly, need to be given a return demonstration at each clinic visit, and need to be provided with reinforcement by the physician or nurse practitioner. Handing out stickers for women to put on their calendars is an effective reminder to perform monthly BSEs. Surely, sending reminder cards a month or two before a date for a mammogram or a CBE will facilitate attention to these important endeavors.

Psychological Counseling

Psychological counseling for a woman who has a family history of breast cancer is extremely important and varies from woman to woman. The potential results of counseling include the following: 1) reduction of emotional distress and anxiety, 2) decrease in perceived vulnerability, 3) change in health beliefs (changing the barrier/benefit screening ratio), and 4) improvement in adherence to screening behaviors. These treatment outcomes follow from what women have defined as the most salient issues, and are a realistic way of improving women's quality of life.

Individual Treatment

Frequently, women who seek individual counseling are those who are primarily concerned with the impending or recent death of their mother or sister. They are seeking psychological support in order to cope, both physically and emotionally, with their relatives' breast cancer. Sometimes women need permission to

take time for themselves and not focus all their energy on being a caretaker. Yet others look for a place in which they can describe all that they are doing for their relative. Women's intrusive thoughts about breast cancer occur on a daily basis, frequently interfere with daily activities, and may continue for years after the death of a relative.

Other women undertake individual counseling because they feel they have no place to turn and they lack the necessary social supports for dealing with their breast cancer risk. Not surprisingly, risk information is repeated many times for women who need to hear their objective medical risk over and over again, as it is incongruent with their perception of risk. Descriptions of a deceased relative in terms of physical appearance, accomplishments, or other attributes may persist for a long period of time. Frequently, this is a necessary component of the healing process. Women's own fears of death and dying are foremost in their minds, most often around the time of an examination for breast cancer.

Psychoeducational Group Intervention

On the basis of our findings from the study mentioned above, we began to investigate ways to decrease the emotional distress of high-risk women, to help them cope actively, and to adhere to early-detection procedures. Because high-risk women increasingly identify themselves and look for programs where they cannot only find appropriate surveillance guidelines but also share their feelings and concerns with others, the efficacy of a group intervention needed exploration. We conducted preliminary studies by piloting a group psychoeducational intervention, based on a self-regulation theory (22,23). This theory was developed by researchers to explain how people cope with stressful situations or how people adapt to health threats.

There were three important components to this 6-week structured intervention. The first was educating women by the following methods: 1) providing them with objective risk status (using the Claus model described above) based on their family tree (pedigree); 2) clarifying information about breast cancer and other risk factors for breast cancer; 3) providing information on ways to take control of their lifestyle by changing their eating patterns; 4) providing instructions on BSE using both active and passive methods; and 5) reinforcing the importance of adherence to screening guidelines. The second component revolved around cognitive restructuring, which helps to facilitate problem solving. That is, we encouraged women to use active coping rather than avoidance or denial in dealing with their risk status. In addition, changing cognitions can help to alleviate anxiety and the sense of helplessness. The last component was that of emotional support that helped to: 1) decrease the sense of isolation, 2) encourage the sharing of feelings and thoughts with others, and 3) provide reassurance by and rapport with other women. After 6 weeks, we were able to decrease perception of risk so it corresponded to accurate genetic risk, correct misconceptions about breast cancer, and increase adherence to screening procedures.

Women were randomly selected and assigned to either the experimental or control condition and assessed for demographic, psychological, social, and risk variables before and after the intervention took place. The interviewer was blind as to which

condition the woman was assigned. There were 10 women in each of the conditions for both the pilot and preliminary studies.

Within the experimental condition there was a significant increase in knowledge ($P<.05$), a significant decrease in perceived risk or susceptibility ($P<.015$), and a significant decrease in perceived barriers to screening ($P<.05$) between base line and 6 weeks (the end of the intervention). Analyses of variances at 6 weeks revealed several changes between the conditions: 1) a significant increase ($P<.005$) on knowledge of breast cancer in the experimental group, 2) a significant decrease ($P<.02$) on perceived barriers in the experimental group, and 3) a significant increase ($P<.03$) on knowledge of the risk factors for breast cancer in the experimental group. For example, at the end of 6 weeks, there were still women in the control condition (30%) who thought that being "hit in the breast" increased one's chances of developing breast cancer.

Because women overestimate their risk, we examined differences between groups and within groups on their objective medical risk and their perception of risk across time. Prior to the group intervention, there was a significant difference between women's perception of their risk (mean perception score, 51%-60%) and their objective risk status (mean objective risk, 31%-40%). This was true for both the experimental ($P<.01$) and control ($P<.003$) conditions. There was no difference between the conditions on perception of risk. At the end of the preliminary trial, there was a significant decrease ($P<.01$) on the perception of risk in the experimental condition, but not the control condition. There was no significant difference in the experimental condition between their perception of risk and objective risk status after the trial ended. However, there continued to be a significant difference between perception of risk and objective risk status (Fig. 3) for the control condition ($P<.02$). All women are provided risk counseling when they enter the program. Thus, it appears that when given a pedigree in a small group setting and a careful explanation of their risk, women who came to the group sessions were able to assimilate this objective information into a scheme and decrease their subjective overestimation of risk. However, the women in the control group ($n = 20$) were worrisome in that their perception of risk continued to increase over time. If we find that this overestimation within the control group continues in our large, randomized controlled trial, we will need to identify ways to intervene with these women.

One of the essential features of these psychoeducational groups is a booster session. The purpose of these sessions is a follow-up to the intervention to provide women with an opportunity to meet again as a group and talk about the ways in which they have used the information to help change their cognitions and adapt their coping skills in everyday life. One of the major components influencing the content of the intervention is social support enhancement. These booster sessions provided such a forum for women to obtain this support. Women were also encouraged to talk about the changes in their fears and worries about breast cancer and their life goals. Over the past 3 years, we have had such sessions for our first pilot group. Adherence to screening was significantly improved ($P<.01$) and has been sustained in the years since the initial group was conducted (Fig. 4).

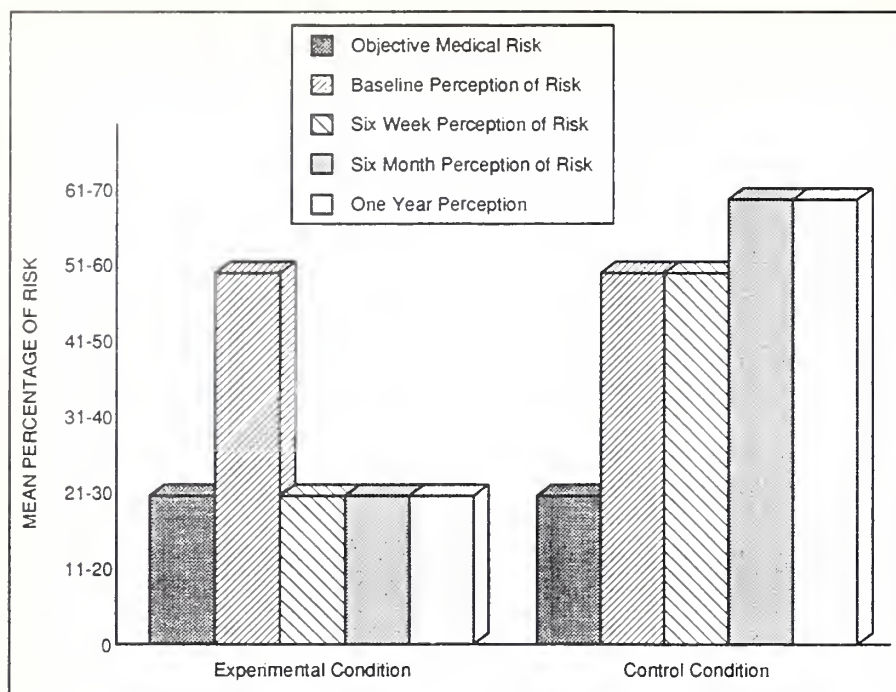


Fig. 3. Comparison of experimental and control conditions on medical risk and perception of risk at base line, 6 weeks, 6 months, and 1 year. Significant difference between experimental and control conditions at 6 weeks, 6 months, and 1 year ($P < .02$).

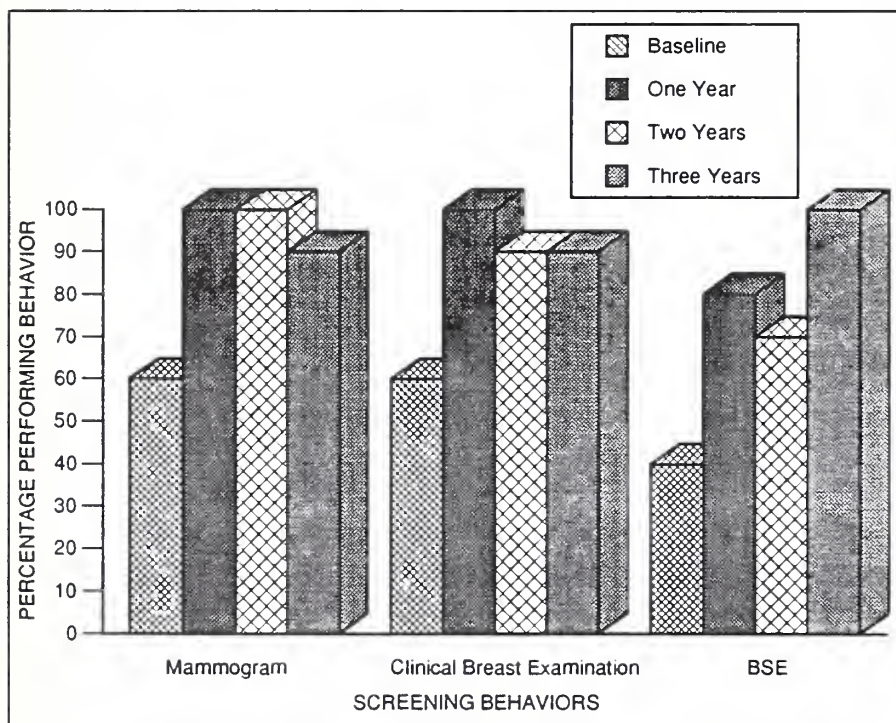


Fig. 4. Percentages of women at high risk of breast cancer adhering to mammogram, CBE, and BSE prior to support group, 1, 2, and 3 years postintervention ($P < .01$).

Conclusion

Women with family histories of breast cancer are at two to three times greater risk of developing breast cancer compared with those who have a negative family history. As women learn about their family histories, they begin to speculate about their own risks. Without adequate information, many women overestimate their risk and become quite fearful that they too could develop breast cancer. We felt compelled to investigate the psychological impact that being at high risk had on these

women. The most intriguing findings from our study were 1) anxiety interfered with adherence to mammogram, CBE, and BSE, and 2) levels of psychological distress equaled those of women who were survivors of Hodgkin's disease and leukemia. This research led us to focus on psychological counseling strategies, particularly group interventions, which may help women cope with being at genetic risk of breast cancer. From these groups, we were able to help women estimate their risk accurately, increase their knowledge of breast cancer, and improve their adherence to screening behaviors. We are presently con-

ducting a large, randomized trial investigating this treatment modality.

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Notes

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Women at Risk of Ovarian Cancer

Jane Wardle*

This paper evaluates perceived cancer risk and worry about cancer among women with genetic risk of ovarian cancer. Women with a first-degree relative with ovarian cancer who were participating in screening were compared with a general population sample who had been screened the previous year and a group of community controls. The results showed that both worry about cancer and perceived risk were higher in the screening groups than in the controls. Estimates of general-population prevalence were on the optimistic side (only 31% estimating that more than one of 10 women would develop cancer in their lifetime) and were unrelated to any psychologic factors, genetic risk, or to personal experience of cancer, but were related to occupational status. In multivariate analyses, perceived personal cancer risk was higher in screening attenders and related to (lower) optimism and knowing more people with cancer. Cancer worry was also higher in screening attenders and associated with lower optimism and a monitoring coping style. [Monogr Natl Cancer Inst 17:81-85, 1995]

Ovarian cancer is the most common and most fatal of the gynecologic cancers. Few significant risk factors have been identified, with the exception of a family history of ovarian cancer that is associated with a greater than threefold risk (1). Genetic studies on the pedigrees of families with ovarian cancer suggest that a single dominant gene with high penetrance is responsible for the predisposition of hereditary ovarian cancer, although on current estimates, fewer than 10% of ovarian cancer cases are hereditary, with the rest being sporadic. Predictive genetic tests are expected to be widely available in the near future.

Publicity about developments in clinical and medical genetics is likely to have alerted people to the possibility that cancer could be an inherited condition, and family cancer clinics already offer estimates of risk. The effect of risk information on anxiety about cancer has attracted scant research attention, although there is widespread agreement that informing people about the risk of a disease that is neither preventable nor treatable is fraught with ethical problems and may have an adverse effect on quality of life. At an individual level, anxiety might motivate some people to attend for screening but deter others. At a population level, the issue is one of weighing the benefits of early detection against the costs in terms of quality of life. In genetic testing for Huntington's disease, there is evidence that the certainty associated with testing is by no means always welcomed, and even negative results may not be perceived as reassuring (2). In anticipation of the development of predictive genetic testing for ovarian cancer, it is important to investigate how anxiety about cancer is generated, who is likely

to be adversely affected, and how to deliver psychologic care where and when it will be most effective.

Green et al. (3) have explored some of the psychosocial issues involved in participation in a United Kingdom familial ovarian cancer register by means of interviews with applicants to the register. Most of the 20 interviewees reported little additional anxiety in response to finding out about the registry, although one woman said that it had made her more anxious and several said that they had been anxious about cancer before hearing about the register. By and large they felt positive about genetic research and welcomed the opportunity to take part. The interviewees had only the haziest understanding of hereditary syndromes, preferring instead to think in terms of dispositions that tended to "run in the family" and which could well be caused by a shared family environment, i.e., they did not necessarily see them as genetic. The authors were concerned that the lack of anxiety observed among interviewees should not result in complacency in the medical community, since the interviewees were among the earliest volunteers to the register and thus might not be typical of the whole group. They argued that early recruits would be more likely to be self-referred, less anxious, and may well have a coping style that rendered them less vulnerable to being emotionally disturbed by the risk information. The implication is that a larger sample of women relatives of patients with ovarian cancer who put themselves forward for further testing might be more anxious and have less effective coping styles. This is evaluated in the present study of recruits to ovarian cancer screening.

Anxiety about cancer is common among women and may even reach pathologic proportions (cancerophobia), casting a blight over the sufferers' lives. The possibility that the development of more cancer surveillance or risk assessment services could increase anxiety still further must be given serious consideration. Evaluation of anxiety levels among women who are made aware of their increased risk of cancer should therefore be an important part of the development of new genetic research on cancer. Equally important is understanding how risk information is processed to explain the wide range of cancer anxiety responses that are observed both in clinical practice and in research. Personal experience of cancer may be one factor that increases the sense of worry. Aspects of personality, such as optimism or coping, which have been shown to be important in responses to

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See "Note" section following "References."

a range of stressful situations, may also moderate perceptions of risk or levels of anxiety and are evaluated in this study.

Since the gene(s) for ovarian cancer have not yet been cloned, individual genetic risk cannot be established with certainty, but pedigree information can be used to generate estimates of genetic risk and the female members of high-risk families can be screened for early signs of ovarian cancer. The best ovarian cancer screening method, at present, is transvaginal ultrasonography combined with various second-stage tests (4). However, ovarian cancer screening raises a number of concerns. There have been no randomized controlled trials to establish the benefits of early detection and treatment of ovarian cancer. Ultrasonography also has a low specificity and therefore generates a high false-positive rate with all the possible attendant anxiety attached to a positive screening result. Little is known about the psychologic processes involved in the acceptance of cancer screening or the meaning of the screening results to the individuals concerned (5). In the breast and cervical screening programs, many eligible women elect not to take the opportunity of screening (6). Research on the emotional responses to positive findings in screening (e.g., cervical intraepithelial neoplasia or benign breast lumps) has found very disparate results. Some studies (7) have identified serious and persistent distress, some find signs of emotional disturbance and worries about cancer but only in the minority of screenees (8,9), and others identify no more than mild and transient concerns (10). The possibility that there are vulnerable groups who are more likely to be disturbed by a positive (or a false-positive) result in screening has been considered by a number of investigators (2,9).

The aim of this paper is to investigate the individual factors that are associated with higher levels of worry about cancer and perception of greater cancer risk among first-degree relatives of women with ovarian cancer. This is one step toward understanding the processes whereby anxiety might be exacerbated or alleviated. This study compares the predictions of anxiety in three different groups: one group comprised women who had a relative with ovarian cancer who were attending for ovarian cancer screening; the second group was a general population sample who had taken part in ovarian cancer screening the previous year; and the third group was a sample of community controls. Both screening groups had responded to national advertising for an ovarian cancer screening program.

Setting

The studies were done in the context of a research unit investigating the use of primary and second-stage screening tests for ovarian cancer among general community volunteers and women who had first-degree relatives with ovarian cancer. Participation was solicited by means of advertising in the local and national press. Women were invited to attend (at their own expense) for an ultrasound scan, and if there was an indication of abnormal ovarian morphology, to reattend for a second scan 6 weeks later at a different stage in the menstrual cycle. If the abnormal ovarian morphology was persistent, women were referred to their own physician for further investigation. They were recommended to have investigative surgery in the hospital

that had done the screening, although this recommendation was not always followed.

Subjects

Ovarian cancer family members. Five hundred women who contacted the screening program in response to advertising for women with a first-degree relative with ovarian cancer were invited to participate in a study of psychologic reactions to cancer screening. Not all of the women who contacted the program eventually attended for screening, so postscreening data were obtained from a smaller group. Postscreening results have been presented elsewhere (9).

General population screenees. Four hundred seventy-seven women who had taken part in ovarian cancer screening (in response to local and national advertising) 1 year previously were invited to participate in a retrospective study of women's reactions to screening. Data on their emotional state in relation to the screening outcome have been presented elsewhere (11).

Controls. Control subjects were recruited from two sources: nominated neighbors of the cancer family members and women from the administrative and technical staff of a London college. The original purpose of the control group had been to ensure that changes observed in the cancer family members over the course of the screening process were not simply due to the passage of time, but base-line data from the control women are presented in this paper for comparisons between first-degree relatives and an unscreened, average risk group.

Measures

Demographics. Age, marital status, occupation, and partner's occupation.

Cancer experience. Number of friends and relatives who have developed, or died of, cancer.

Perceived cancer risk. Personal risk of cancer based on Wellisch et al. (12) (rated as very unlikely, unlikely, likely, very likely, from 1 to 4); general risk of cancer (1/5, 1/10, 1/15, 1/25, 1/50, 1/100, scored from 1 (low) to 6 (high) for some analyses).

Cancer worry. Worry about cancer in breast, cervix, lung, bowel, and "generally" were each rated from 0 (not at all) to 4 (a great deal), with an overall score derived from the sum (range, 0-20).

Optimism. The Life Orientation Test (13).

Coping style. The shortened version of the Miller Behavioral Style Scale (14).

Emotional well-being. General Health Questionnaire (GHQ) (15).

Health attitudes. Ratings of the importance of a range of health behaviors (summary score) based on a measure used in the European Health Behaviour Survey (16).

Results

The data presented here are from 920 women who completed the measures. Three hundred fifty-eight (72%) of the 500 women who had expressed interest in the ovarian family screening returned the questionnaires. Most of the nonresponders were women who decided not to participate in the screening. Ques-

tionnaires were returned by 379 (79%) of the 477 women from the general population sample who had taken part in screening 1 year previously. Some of the nonresponders were likely to have changed address in the intervening year, but we were only able to use the address in the screening records. Response rates were lower in the control women (53%), probably because of the lack of salience of the project for them.

The analyses were directed toward the following: 1) differences between family cancer members, general population screenees, and controls; 2) the evaluation of the influence of experience of cancer, dispositional optimism, mood, and coping style on perceived cancer risk and worry about cancer; and 3) the influence of experience of cancer, perceived cancer risk, dispositional optimism, and coping style in response to false-positive results in cancer screening.

Demographic and Background Psychologic Characteristics

In terms of demographic characteristics, the control women were not perfectly matched to the screenees. Control women were slightly younger ($F[1,873] = 55.2$; $P < .001$) and more likely to be in professional jobs than the screenees ($\chi^2 = 52.7$; $P < .001$), so where appropriate, controls for these characteristics were included in the analyses. There were no group differences in the background psychologic variables of psychologic well-being, optimism, or coping style (monitoring score), although there was a trend toward the cancer family screenees being more emotionally distressed (Table 1). The one exception was the rating of the importance of health behaviors (such as health checks, dietary precautions, and screening), which were rated as more important both by women who had been to the screening and by the prospective screenees than by the controls ($F[1,689] = 3.4$; $P < .05$).

Cancer Experience

As expected, compared with the general population sample or the controls, first-degree relatives had known more people with cancer ($F[2,849] = 12.4$; $P < .001$). The general population screenees had also known more people with cancer than the

controls. Both screening groups had experienced more cancer deaths than the controls ($F[2,843] = 8.13$; $P < .001$) (Table 2).

Perceived Cancer Risk and Worry About Cancer

Perceptions of personal cancer risk placed most women in the likely (59%) category. There was a significant group difference in the mean ratings of personal chance of cancer ($F[2,852] = 27.00$; $P < .001$), with women in the two screening groups judging themselves as more likely to develop cancer than the controls. There was no significant difference between the two screening groups (Table 2).

In terms of the population risk, most women selected one of five (31%) or one of 10 (31%) as the proportion of women who would be likely to develop cancer at some time in their life. There were no significant group differences.

Worry about cancer significantly differentiated the groups ($F[2,852] = 56.8$; $P < .001$), but was highest in the women who had attended screening 1 year earlier (Table 2).

Predictors of Perceived Risk of Cancer

Potential predictors were evaluated first in terms of univariate associations and then multivariate associations, with screening attendance and genetic risk group as independent variables.

In all three samples, the perception of personal risk of cancer was related to personal experience of cancer. Deaths by cancer among friends and relations were divided into 0, 1, 2, 3, and 4 or more. Women who knew more people who had died of cancer rated their own cancer risk higher ($F[4,806] = 4.6$; $P < .001$), with mean scores of 2.45, 2.79, 2.88, 2.99, and 3.07, in the respective groups. The effect was found in screenees and controls but was stronger in the two screening groups than in the controls (group by number of deaths interaction: ($F[8,806] = 2.3$; $P < .05$).

Perception of personal risk of cancer was related to dispositional optimism, with a negative correlation between optimism and perceived cancer risk across the whole group ($r = -.20$; $P < .001$). Correlations computed separately for each sample were very similar ($r = -.17$, $-.21$, and $-.22$). Psychologic well-being (GHQ score) was also related to perception of risk of cancer ($r = .15$; $P < .001$), but there was no significant association with coping style or with any of the other background variables.

Table 1. Background characteristics (mean \pm SD)

	Family cancer prospective screenees (n = 358)	General population postscreenees (n = 378)	Controls (n = 186)
Age, y, mean \pm SD	49.55 \pm 9.75	52.38 \pm 9.36	43.32 \pm 10.18
Higher social status (combined), %	54.3	58.6	67.9
Optimism (range, 0-32), mean \pm SD	19.83 \pm 5.07	20.37 \pm 4.93	20.40 \pm 5.07
Monitoring (coping) score (range, 0-8), mean \pm SD	4.05 \pm 1.69	4.07 \pm 1.69	4.17 \pm 1.77
Total GHQ (range, 0-28), mean \pm SD	4.41 \pm 5.88	3.78 \pm 5.06	3.62 \pm 5.04
Rating of importance of health behaviors (range, 13-130), mean \pm SD	108.55 \pm 14.08	109.03 \pm 14.24	104.54 \pm 14.48

Table 2. Cancer experience, cancer risk, and worry about cancer

	Family cancer prospective screenees (n = 358)	General population postscreenees (n = 378)	Controls (n = 186)
No. of friends/relatives with cancer, mean \pm SD	2.83 \pm 1.65	2.50 \pm 1.57	2.06 \pm 1.67
No. of friends/relatives who died of cancer, mean \pm SD	2.37 \pm 1.51	2.17 \pm 1.38	1.79 \pm 1.60
Personal cancer risk (range, 1-4), mean \pm SD	2.96 \pm 0.69	2.94 \pm 0.64	2.53 \pm 0.69
Cancer worry (range, 0-20), mean \pm SD	11.19 \pm 3.16	13.92 \pm 4.36	10.78 \pm 2.87
Population risk (range, 1-6), mean \pm SD	4.31 \pm 1.61	4.57 \pm 1.54	4.50 \pm 1.37

For the stepwise multiple regression, dummy variables representing screening participation (screenees versus controls) and genetic risk (ovarian family cancer group versus others) were created. Screening participation, number of deaths experienced, optimism, and psychologic well-being (GHQ score) all contributed significantly to the perception of the risk of cancer (Table 3).

There was no evidence that the estimated population risk of cancer was related to experience of cancer, participation in screening, or to any of the background variables. However, it was related to occupational status, with women in higher social status occupations rating the population cancer risk as higher ($F[4,725] = 3.50$; $P < .01$).

Predictors of Cancer Worry

In univariate analyses, worry about cancer was negatively related to optimism ($r = -.24$; $P < .001$) and positively to GHQ score ($r = 0.16$; $P < .001$), perceived risk of cancer ($r = .33$; $P < .001$), and monitoring style ($r = 0.14$; $P < .001$), but not to number of deaths or to any other background variables.

These effects were largely confirmed in a multivariate analysis, in which all of the above variables independently contributed to cancer worry, as well as there being more worry among women in the screening groups than the controls, but less worry among the genetic risk group than the others (Table 4).

Predictors of Responses to Positive Screening Outcomes

Data presented in a previous publication have indicated the importance of coping style among the ovarian family group in predicting responses to positive results at the first ultrasound scan (9). Women whose base-line coping style questionnaire

placed them in the high-monitoring group (Miller monitoring score > 4) showed much greater deterioration in well-being after a false-positive result than women in the low-monitoring group. Very similar results were obtained in the general population group who were evaluated 1 year after screening (11); among women who had received a false-positive result, the group with high-monitoring scores had higher GHQ scores (poorer psychologic well-being) than women with low-monitoring scores.

In the light of the analyses presented earlier, responses to the scan results among the ovarian cancer family group were also evaluated in relation to cancer experience and optimism. However, there was no evidence that the change in GHQ scores after the first scan was related either to optimism, past cancer experience, or initial level of perceived cancer risk. Background psychologic characteristics other than coping style were therefore not strongly predictive of acute responses to positive screening results. Likewise, no other psychologic factors were found to be significant in the general population group.

There was some evidence of differences in the degree of reassurance experienced by women in the family cancer group who received negative screening results in relation to optimism. There was a significant relationship between optimism and worry after the scan (have you worried more, the same, or less since the scan?) ($\chi^2 = 6.2$; $P < .05$). Optimists (those scoring in the upper half of the optimism scale) were more likely than pessimists to respond to a negative result by feeling "less worried" (35% versus 21%), while pessimists (low scorers) were more likely to describe themselves as "the same" (68% versus 53%). In relation to past experience of cancer and coping style, however, there were no significant effects.

There was a similar pattern of results among the retrospective group ($\chi^2 = 6.7$; $P < .05$), with more optimists feeling less worried (51% versus 36%) and more pessimists staying unchanged (61% versus 47%).

Discussion

The data described in this study had been gathered in the context of a study evaluating women's responses to false-positive results in ovarian cancer screening (9,11,17). The aim of the present analyses is to shed more light on the factors influencing women's perceptions of risk of cancer and level of worry about cancer, since these are serious issues in connection with both cancer screening and predictive genetic testing. Of particular concern was whether the predictors of anxiety in first-degree relatives were the same as in lower-risk groups.

As a group, women who had responded to the screening advertising for members of ovarian cancer families perceived their own likelihood of developing cancer as higher than the controls (perhaps correctly). For some of these women, the advertisement was their first realization that ovarian cancer might be inherited (17). However, their higher ratings of cancer risk were shared by the sample of general-population women who had taken part in screening the previous year. This suggests that the perception of personal cancer risk is related to the fact that these are all women who had decided to seek screening. Whether perception of cancer risk is higher among women from ovarian

Table 3. Summary of multiple regression with chance of cancer regressed onto the cancer experience and psychologic variables*

Variable	B	β	Student's <i>t</i> test value	P
Ovarian cancer family member	-.000	-.000	0.007	NS†
Screening participant	.35	.20	-5.48	.001
Optimism	-.02	-.17	-4.97	.001
GHQ score	.01	.09	2.50	.01
Deaths experienced	.04	.10	2.86	.004

*Multiple $R = .327$; $R^2 = .107$; F ratio = 19.21; $df = 5, 802$; and $P < .001$.

†NS = not significant.

Table 4. Summary of multiple regression with cancer worry regressed onto the cancer experience and psychologic variables*

Variable	B	β	Student's <i>t</i> test value	P
Ovarian cancer family member	2.85	.35	9.73	.001
Screening participant	-2.5	-.24	-6.76	.001
Optimism	.13	.17	-4.88	.001
Monitoring	.24	.11	3.14	.002
GHQ score	.04	.05	1.61	.11
Chance of cancer	1.36	.24	6.75	.001

*Multiple $R = .518$; $R^2 = .268$; F ratio = 35.24; $df = 7, 672$; and $P < .001$.

cancer families who have not elected to seek screening cannot be established from these data.

The data revealed a clear effect of the experience of cancer on perception of risk in all three groups, with women who had experienced more cancer among their friends and relatives perceiving cancer as more likely for them personally. This may relate to the observation by Green et al. (3) that people tend to think that cancer runs in the family (or possibly even in people from similar backgrounds), regardless of their understanding of genetics. An alternative is that cancer experience of any kind causes women to increase their estimate of risk, but against this interpretation is the fact that estimates of population risk were unrelated to personal experience of cancer.

Independently of cancer experience, the personality trait of optimism was strongly associated with lower personal cancer risk estimates and less worry about cancer (although not with lower population risk estimates) in all three groups. This suggests that there are some people (life's pessimists) who are inclined to see the hazard of cancer as likely to happen to them (just as they see all kinds of negative events as more likely), and there are other people (the optimists) who are less likely to believe that bad things will happen to them. In the present dataset, optimism was also associated with greater reassurance after negative screening results in both first-degree relatives and population screenees. The mechanism whereby optimism induces bias in risk assessment is an important aspect of psychologic research in screening.

Curiously, ratings of population cancer risk, although showing considerable variability over the sample, were unrelated to any of the background psychologic variables. However, cancer prevalence was rated as higher by women in higher social status occupations. The most likely explanation for this observation is that higher social status occupations are associated with better education, which would mean better health knowledge and hence more awareness of the state of public health.

Coping style (monitoring score) was no higher in the screenees than in the controls [contrary to the suggestion of Green et al. (3)] and was unrelated to estimates of cancer risk in any of the samples, but higher monitors were more worried about cancer and responded less well to positive results in ovarian cancer screening (9,11).

The present results suggest common influences on perceptions of risk and worry among women with a first-degree relative with cancer and lower risk groups. The study was not designed to evaluate genetic screening, but on the basis of previous work with first-degree relatives of ovarian cancer patients (18), it is likely that the first-degree relatives in this sample would be the same kind of women who would express interest in predictive genetic testing. The development of the new genetics raises a host of important psychologic questions, including understanding how the decision to be tested is reached, how risk information is assimilated and coped with, how health professionals should communicate information about genetic

risk, and what strategies might be used to identify and manage distress. The present results emphasize the importance of considering both the individual's coping style and her experience of cancer as predictors of her response to risk information. The challenge for psychologists is to help to steer a pathway through the development of new technologies, which enhance, rather than detract from, quality of life. Closer research links between geneticists and health psychologists will be an important element of the research strategy.

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Genetic Testing: Employability, Insurability, and Health Reform

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Presently, 85%-90% of individuals with private health insurance are covered under group health insurance, with most covered through employment. Under virtually any system of health care reform likely to be enacted in the near future, employers will continue to play a major role in the funding of private health care. As costs of health care are increasing dramatically, employers and insurance carriers are examining alternatives for controlling health care expenditures. Not all consumers of health care are equal in their rates of consumption. Tremendous savings could be realized by parties responsible for paying for health care if the most expensive (or potentially most expensive) health care users could be identified and their costs shifted to another payer. Genetic testing could play a major role in predictive health screening to identify individuals with the potential for developing cancer. This prospect raises three major problems regarding employability and insurability. First, individuals could be subject to discrimination in employment, with the responsibility for their health coverage shifted to the public sector. Second, privacy and confidentiality could be compromised through the compilation, storage, and release of non-job-related, sensitive medical information. Third, the fear of employment discrimination through employer access to medical records generated in the clinical setting might discourage at-risk individuals from undergoing medically indicated genetic testing. This report reviews these issues and emphasizes that these concerns must be addressed in the context of health care reform as well as through the interpretation of existing legal proscriptions on employment discrimination. [Monogr Natl Cancer Inst 17:87-90, 1995]

A major consideration in issues of genetic testing and employability or insurability is the existing relationship between health insurance status and employment. Under our current health care system, 85%-90% of individuals with private health insurance are covered under group health insurance. Most of these individuals are covered through their work, either as employees or as dependents of employees: only 10%-15% of people have individual health insurance policies, and only about 10%-15% of people have health insurance through groups that are not employment related (1). Thus, employment continues to play a very important role in whether an individual has health insurance status; employers will continue to play a major role in the funding of private health care under virtually any system of health care reform likely to be enacted in the near future.

Health care costs have increased dramatically in recent years. By any measure (e.g., total expenditures, percent of Gross Domestic Product, per-employee cost, percent of payroll costs, rate of increase, and percent of corporate profits), increasing costs present a major problem to the health care system and to the nation. The following examples are different ways of expressing the same thing: our health care system is increasingly expensive and, in terms of the payer's perspective, at the breaking point.

Health care costs are roughly \$1 trillion per year now and are on the rise: by the year 2000, the United States will be spending about \$1.6 trillion per year on health care. This increase can be expressed as the per-employee cost of health care. The per-employee cost of health care for employers has doubled in 6 years; it is now well over \$4000 for the average employer and in the \$6000 range for companies with more generous benefits (2).

Expressing health care as a percent of total compensation paid by employers is another way of demonstrating the same phenomenon. This was a tiny fraction, 0.3%, after World War II. It has continued to grow over the years and has doubled in most decades, increasing from 1.1% in 1960 to 2.3% in 1970, 4.4% in 1980, and 6.3% in 1990 (3).

Another way of expressing costs of health care is as a percent of pretax profits for employers. By the year 2000, business expenses for health care will represent 74% of pretax profits (4).

So naturally, corporate America looks at these figures and is compelled to action. The Louis Harris survey finding that 87% of managers felt some or a great deal of pressure to control health care costs should come as no surprise whatsoever (5); the question is how to accomplish cost control.

Health Care Cost Control

Basically, there are six traditional methods of reducing health benefit costs. The first method is the simplest and the easiest. There is no law that requires an employer to offer health insurance; indeed, many small companies cannot afford to and do not offer health care benefits at all.

A second method is to limit the coverage for certain individuals. For example, health insurance coverage for retirees who are below Medicare age may be canceled unless there is a contract, such as a union collective bargaining agreement; most courts have upheld this as legal. Other employers limit or

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eliminate dependent coverage, so that costs are not shifted from one employer to another.

A third possibility is eliminating coverage for certain medical conditions. Mental health and substance abuse are examples of illnesses or conditions for which cost to employers has increased tremendously during the last decade. Caps may be placed on specific conditions, or coverage for the conditions may be eliminated altogether. This is in addition to the old insurance concept of barring coverage for pre-existing conditions (for a specified period of time or forever), which can result in "job lock."

Fourth, the percentage that employees contribute may increase annually through higher deductibles, higher copayments, and so forth. A fifth approach that has been used is managed care (accomplished by forcing employees into Health Maintenance Organizations, Preferred Provider Organizations, point of service operations, or other similar systems) that requires pre-treatment authorizations, preadmission evaluations, or second opinions as a method for reducing costs.

Finally, the option of self-insurance is a particularly attractive alternative for employers. Basically, employers can offer health care coverage to employees in one of two ways. They can purchase an insurance contract from a commercial insurance company such as Aetna, Prudential, and Travelers. However, these contracts are regulated by state health insurance laws, and many of them mandate coverage for certain conditions and restrict the flexibility that employers have. Alternatively, an employer can become self-insured (i.e., it pays for the health care expenditures of employees, dollar for dollar, out of its general revenues) and thus avoid many of these problems.

What we see currently is a splitting of the health care coverage market in which very large companies are almost all self-insured, very small companies offer no insurance, and medium-sized companies scramble to find health care coverage at reasonable rates through commercial insurers. The latest breakdown of the percentage of self-insurance by employer size shows that nearly 90% of the largest companies are self-insured (6). It also shows that there are a number of very small companies that are self-insured, despite having too few individuals covered to spread the risk around. A few catastrophic illness claims could conceivably wipe out some of these small businesses, and even some of the larger companies. Keep in mind that the original Clinton plan for health care reform would have set a cutoff at 5000 employees and would have allowed employers with 5000 or more employees to continue self-insurance, while the Cooper plan would have set the limit at 100 employees. While different cutoffs are under discussion, it is obvious that employers will continue to play a role in health care finance in this country and that self-insurance will remain as an alternative for many.

Yet another consideration in health care cost control is that not all consumers of health care are equal in their rates of consumption. In any given year, 5% of consumers account for 50% of health care expenditures, and 10% of health care users account for 70% of expenditures (7). For a party responsible for paying for health care, if the most expensive (or potentially most expensive) health care users could be identified and their costs shifted to another payer, then tremendous individual savings

could be realized. For example, health insurance companies decline coverage for the riskiest individuals or assign them higher rates. This practice may result in individuals, such as those with pre-existing conditions, or entire groups, such as small employers, being unable to obtain health insurance (8). This feature of private health insurance—denying coverage to those who need it most—is one of the few parts of the current health care system that all parties agree needs to be changed.

Health risk selection has become increasingly attractive for insurance companies, and self-insurance may increase the incentive for employers to exclude high-cost users from coverage (9). There is considerable concern that the incentive to discriminate in coverage will merely be shifted from insurance companies to employers, who will effect this discrimination by not hiring persons perceived to be high-cost users of health care, such as persons at increased risk of heart disease or cancer.

Genetic Testing: Policy Goals

Genetic testing could play a major role in enabling identification of persons with an inherited predisposition to develop cancer. Think about it: if you are the payer of someone else's health care benefits, it would certainly be in your economic interest to avoid covering any person who you knew in advance was highly likely to develop cancer, thus avoiding all of the costs attendant to diagnosis and treatment of that condition. Insurance companies can avoid these costs by not offering insurance to that individual. Individual health insurance policies can simply deny coverage or place exorbitant rates on such individuals. However, if you are an employer, the only way to avoid covering such individuals under your group plan or through your self-insured plan is not to employ them. So, if you have a few potentially high-cost health care users, and you can figure out who they are, there is a tremendous incentive to dismiss these individuals or not hire them at all.

With that as a premise, we have to consider the policy implications and try to develop goals that will realize the policies we want. Ten goals are listed below.

First, we clearly do not want to discourage people who want to be tested from doing so. There are many people who may be at increased risk of cancer because of an inherited cancer-related gene who would want to undergo genetic testing to determine the need for prophylactic intervention; they might not undergo testing if they thought the results could make them unemployable and, therefore, uninsurable.

Second, on the other hand, we do not want to coerce people who do not want to be tested into genetic testing. This could happen if, for example, an employer were to require genetic testing as part of a preplacement medical examination.

Third, we want to perform genetic testing only for the benefit of the person tested. This point has been clearly emphasized by the Institute of Medicine in its recent report on health and social policy implications of assessing genetic risks (10). This axiom extends beyond the context of employment and insurance into many other areas of health.

Fourth, we want to preserve the quality of all testing and counseling. And, if testing is done for the benefit of someone who is not the patient, then I think we can infer fairly that the

counseling that we think is important will not be performed at the level that we would want.

Fifth, we also want to conserve medical resources. There are a finite number of clinical geneticists, a finite number of genetic counselors, and a finite number of health care dollars. Why should we use these resources for nonmedical purposes?

Sixth, we must maintain the confidentiality of medical records. We need to prevent employers from gaining access to records of genetic testing, irrespective of whether adverse employment decisions will result. Concern about confidentiality is one reason that people do not seek genetic testing and counseling. We also want to preserve the physician-patient relationship and not have it undermined.

Seventh, we want to avoid unfairly stigmatizing people by labeling them as cancer gene carriers or as predisposed to develop malignancies. This is based on the assumption that it is unfair to deny people jobs because of the statistical probability that they may develop an illness at some point in the future. This is linked to the eighth point, that we do not interfere with equality of opportunity.

Ninth, such discrimination in employment would be a terrible waste of human resources by our country. Can you imagine an employer who might say, "This person has the BRCA1 breast cancer gene and therefore is at an 85%-90% risk of developing cancer. Treatment with high-dose chemotherapy/autologous bone marrow transplants costs \$100 000-\$150 000 (11). We cannot afford to employ that person." What if no one wanted to employ that person? Here is someone who is potentially productive, but whom no one will hire. The taxpayers are not only going to pay for the health insurance coverage through the public system for that individual, but they are also going to have to pay for income replacement or welfare to have this person sit at home and do nothing.

And tenth, of course, is that we want to avoid the secondary consequences of discrimination by employers based on genetic testing, such as loss of insurance or "job lock."

Strategies to Prevent Discrimination

What should the strategies be for preventing genetic discrimination in employment? I would argue that genetic testing by employers for occupation-related traits must be limited to very narrowly defined, job-related conditions. As the Office of Technology Assessment's report concluded, there is very little evidence that occupationally related genetic testing is of major efficacy (12). While there may be a reason for genetic studies as a measure of exposure to occupational hazards, for example, cytogenetic monitoring of workers in nuclear materials production, exclusions on the basis of genetic testing must be extremely limited (13).

Second, genetic information generated by an employer or stored within his or her files must be kept confidential. This is the problem of redisclosure.

Third, testing for nonoccupationally related genetic traits, including most of the cancers discussed at this meeting, should be prohibited and employment decisions should not be based on genetic factors. To accomplish this, I would suggest that

employers should not be permitted access to medical records of genetic tests generated in the clinical setting.

Unfortunately, the current law addressing health-based discrimination, the Americans With Disabilities Act (ADA), does not expressly incorporate these suggestions. In fact, there is some evidence of a contrary interpretation, at least at the moment. What we are concerned about at this meeting is the situation in which a genotype indicates a predisposition or increased risk to later onset of a disorder that may become a disability as defined by the ADA. If the disorder is not an active disability according to the ADA definition, the individual is not covered. The current interpretation by the Equal Employment Opportunity Commission, the federal agency that enforces the ADA, is that until persons genetically predisposed to disease become symptomatic, there is no coverage. We hope that interpretation will be changed before too long (14).

A specific problem area is screening for non-job-related genetic conditions of individuals after a conditional offer of employment. While this is legal under the ADA and thus genetic testing would be lawful, 11 states have laws prohibiting this.

An important point is that employers do not have to do their own testing. They can get genetic information from tests that are performed in the clinical setting by requiring conditional offerees and employees to sign releases for their medical records, such as at preplacement medical examination or a return-to-work physical, and through health insurance claims. When an employee files a claim, a self-insured, self-administered employer knows exactly what the employee is being treated for.

Political Questions

This raises three political questions. First, should legislation be enacted at the national or local level in response to the problems outlined above? Second, should the law regulate the access to genetic information or the use of the information? Third, should separate genetic discrimination laws be passed, as nine states have done in the area of employment discrimination, or should this be included as part of a broader antidiscrimination law? Does separate legislation further stigmatize genetic diseases? How should legislation deal with the very thorny definitional problem of what constitutes a genetic condition? Perhaps a better approach is to redefine and restructure antidiscrimination laws in general to include these issues.

With regard to health care reform, the first question is not at issue: the word "genetic" does not appear in any of the plans. The National Institutes of Health are concerned that appropriate genetic services be made available to all. In addition, it is imperative to safeguard autonomy in reproduction, expand professional and public education, prohibit genetic discrimination by both health insurers and employers, and protect the confidentiality of genetic information. This would be a great starting point for health care reform.

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Defining, Identifying, and Studying High-Risk Families: Developing Cohorts for Epidemiologic Study

David P. Harrington, Alice S. Whittemore*

Many issues arise in planning epidemiologic studies of individuals at high risk for developing hereditary cancers. The most important are (a) determination of the information that can best be studied in epidemiologic settings; (b) selection of proper study designs; (c) acknowledgment of the ethical, psychosocial, and legal issues that will arise in these studies; and (d) anticipation of the logistical issues involved in large, multicenter studies. The breakout session "Developing Cohorts for Epidemiologic Study: Defining and Identifying High-Risk Families" examined these issues, and the results of that session are summarized here. There was general consensus that little information exists regarding the prevalence of genetic mutations that predispose individuals to increased cancer risk, the risks conferred by specific mutations and by gene-environment interactions, and the efficacy of potential interventions. Adequately controlled observational and randomized studies provide the best mechanism for obtaining this information, despite the considerable ethical and strategic difficulties that will arise in the planning and conduct of such studies. [Monogr Natl Cancer Inst 17:91-94, 1995]

This paper summarizes the discussion at the breakout session "Developing Cohorts for Epidemiologic Study: Defining and Identifying High-Risk Families," conducted at the National Cancer Institute Workshop on Hereditary Breast, Ovarian, and Colon Cancer, held April 26-27, 1994. The session focused on four issues facing investigators studying hereditary cancers:

- Identifying the information best gained from epidemiologic studies of individuals with high risk of hereditary cancers;
- Selecting study designs appropriate for study objectives;
- Assessing the impact of ethical, psychosocial, and legal issues on study objectives and designs; and
- Planning for the logistic and feasibility issues that will arise in cohort studies of high-risk families.

These issues are not limited to studies of breast, ovarian, and colon cancers; they also arise in the study of all site-specific cancers with a strong hereditary component. Because of the prevalence of breast and colon cancers, however, most of the discussion at this session was devoted to those diseases.

The problems that investigators will face in conducting research in this area are formidable, and the issues that must be resolved (*described below*) may seem discouraging. We do not believe that these issues are insurmountable, but they will require creative and innovative solutions.

Information Needed From Epidemiologic Studies

Currently, the scientific community has the following needs: (a) more information on the mutational spectrum of genes that increase cancer risk as well as population-based estimates of the prevalence of these mutations; (b) more precise and accurate estimates of the age-specific and lifetime risks among carriers of mutated alleles; (c) estimates of the effect of environmental and lifestyle factors on cancer risk in gene carriers; and (d) data on the efficacy of prophylactic interventions for risk reduction in carriers.

(a) **Prevalence of genetic mutations that confer increased risk of cancer.** Such estimates are essential in planning intervention studies and in assessing the fractions of cancer cases attributable to genetic and lifestyle factors.

(b) **Risks in carriers.** The data from linkage studies of breast and ovarian cancers indicate substantially increased risks of these malignancies among carriers. However, these studies are based on data from families with multiple cancers, and they may overestimate both the risks in carriers drawn randomly from the population and the more specific risks among carriers from families with a smaller incidence of cancer. Even more specifically, the scientific community needs information on the effect of specific mutations on risk.

(c) **Effects of environmental and lifestyle factors on risk in carriers.** At present, there are little or no data on this issue. Yet such data are needed in planning intervention studies. Adequate power to address this issue will require large studies involving many carriers who have been both exposed and unexposed to the risk factors of interest.

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See "Notes" section following "References."

(d) **Effectiveness of interventions.** Few data on this issue exist at present. The following are the most important questions regarding interventions: How much does prophylactic mastectomy reduce the lifetime risk of breast cancer in members of high-risk breast cancer families? How effective is mammography in preventing breast cancer mortality among high-risk women, especially young women, and what are the long-term risks from radiation exposure in this group? What are the benefits and risks of prophylactic oophorectomy in women at high risk for ovarian and/or breast cancer? How effective are oral contraceptives in reducing ovarian cancer risk in high-risk women? How effective are dietary supplements of calcium or folic acid in preventing colon cancer in carriers of specific mutations of predisposing genes for hereditary nonpolyposis colon cancer (HNPCC)?

Study Designs

Several designs were discussed for studies that address the above issues. These designs include the following: cross-sectional studies based on stratified samples of diseased and asymptomatic individuals, cohort and case-control studies sampled from the general population, cohort studies of identified high-risk individuals, and randomized trials comparing interventions designed to reduce cancer incidence. Table 1 summarizes some of the strengths and weaknesses associated with each of these designs. Moreover, the choice of design will be determined by the specific hypothesis to be tested and by the

ethical, legal, and psychosocial issues outlined in the section below.

Cross-sectional studies based on random, stratified sampling from a population are the most natural ways to estimate the prevalence of a genetic mutation. Such studies provide unbiased estimates of prevalence rates both for the whole population and for strata defined by characteristics such as age or ethnicity. Cross-sectional studies will be difficult in this area, however. The relatively low prevalence rates will lead to poor positive predictive value of a diagnostic test (i.e., the probability that an individual is a true carrier, given that a diagnostic test is positive). For the next few years, diagnostic tests for the HNPCC genes and for the BRCA1 gene are likely to be expensive and to have lower sensitivity and specificity than are desirable.

Case-control studies can be used to estimate the increases in risks of cancer associated with specific germline mutations, as well as the proportions of cancer incidence attributable to those mutations. Such studies, however, must sample case patients and control subjects from a broad spectrum of population strata, must have access to DNA testing for both case patients and control subjects, and must gather extensive data on environmental and other risk factors. Case-control studies may provide approximate estimates of the population prevalence of specific genetic mutations from control subjects, but those estimates may be biased by the lower prevalence of carriers in a disease-free population. The sampling frames of such case-control studies preclude using them to estimate risk among carriers. Only very large studies will contain enough carriers to evaluate gene-environment interactions.

Table 1. Strengths and weaknesses of designs for studies of high-risk families

Design	Characteristic	Strength	Weakness
Cross-sectional studies	Random sampling of DNA and risk factors from a subgroup of the population	Can give unbiased estimates of mutation prevalence	Cannot estimate cancer risks associated with specific mutations
Case-control studies	Individuals with cancer (case patients) and without cancer (control subjects) are evaluated for mutations of predisposing genes and for cancer risk factors.		Case patients and control subjects may differ with respect to other unmeasured genetic characteristics.
			Large studies are needed for power to detect "gene-environment" interactions.
	(a) Within high-risk families	Relatively short time frame Large numbers of carriers are available for study.	Unbiased evaluation of intervention efficacy is unlikely.
	(b) In other subgroups of the general population	Population-based estimates of mutation prevalence are possible.	Few mutation carriers are available for study of gene-environment interactions.
Cohort studies	Asymptomatic individuals provide DNA and data on risk factors; they are then monitored for cancer occurrence.		Longer time frame than case-control studies; expensive
	(a) Within high-risk families	Large numbers of carriers are available for study.	Unbiased evaluation of intervention efficacy is unlikely.
	(b) In other subgroups of the general population	Population-based estimates of specific mutations are possible.	Few mutation carriers are available for study of gene-environment interactions.
Randomized trials	Asymptomatic individuals are randomly assigned to one of two or more active interventions to prevent cancer occurrence or to detect it at an early stage.	Comparisons of treatment efficacy are unbiased.	Costly design
	(a) In members of high-risk families		Insufficient numbers of carriers for adequate precision in comparing treatments
	(b) In carriers of mutations		

The questions addressed by a case-control study also can be addressed by a cohort study of a representative sample of the general population. In addition, such cohort data allow unbiased estimates of mutation frequencies and unbiased estimates of age-specific and lifetime risks.

In principle, *cohort studies of identified gene carriers* can be used to estimate age-specific and lifetime risks, but such studies will face many challenges. Unbiased estimates of risk require registries with data on a true random sample of carriers. Most existing registries of high-risk families contain families selected for the existence of multiple cancers; therefore, the cancer experience in these families will tend to overestimate risk in the general population. Since risk is likely to be influenced by both environmental factors and subsequent interventions, observational studies must gather extensive data on risk factors, as well as longitudinal measurements on interventions and changing lifestyles.

It is unlikely that observational cohort studies of carriers can be used to measure the relative benefit between two interventions. Bias can arise in an observational study of interventions when patients at higher risk select more aggressive interventions, as might be the case, for example, if patients with BRCA1 mutations and with a high incidence of familial breast cancer tend to select prophylactic mastectomy more often. Bias can also arise if large treatment centers that see a disproportionate share of high-risk patients offer only a single intervention option to identified carriers.

The feasibility of *randomized trials* to compare interventions depends strongly on the disease and on the estimated risk of the study participants. The problem of conducting a randomized trial comparing interventions in breast cancer is particularly acute. Prophylactic mastectomy would almost certainly be one arm of a randomized intervention trial in breast cancer, since no definitive study has established the value of that procedure or weighed its value against the associated morbidity and psychosocial implications. The choice of a second arm, however, presents difficulties. There is no widespread agreement on a potentially effective, nonsurgical intervention for young, high-risk women. With the recent sequencing of BRCA1, it seems inevitable that the scientific community must soon decide whether to begin a study of mastectomy versus a no-treatment control arm, with aggressive screening, in carriers of mutations. Such a trial confronts serious ethical issues.

There are more options for randomized trials of interventions in carriers of the genes for HNPCC. There is a strong rationale for nonsurgical interventions such as dietary supplements with calcium or folic acid, and colonoscopy followed by sampling of the mucosal wall of the colon can be used for the periodic evaluation of study subjects.

Current trials in the prevention of breast or colon cancer may present the opportunity to identify and study interventions in high-risk individuals, but such an opportunity also encounters difficulties. Since the current tamoxifen-versus-placebo breast cancer prevention trial selects women with a family history of breast cancer, the prevalence of BRCA1 carriers in that trial will be higher than in the general population. The randomization in that trial should allocate roughly equal numbers of women with

a BRCA1 mutation to each intervention, allowing an unbiased comparison between the two interventions.

This strategy has several disadvantages, however. First, the breast cancer prevention trial may not be large enough for such a subset analysis, even with its planned 16 000 registrations. Current estimates suggest that the population prevalence of BRCA1 mutations may be as high as 1/200. If the prevalence of BRCA1 mutations in this prevention trial is even twice this value, then about 160 women with BRCA1 mutations will have been registered in the trial. The inclusion of 80 women per treatment group will not provide enough precision to detect a tamoxifen benefit unless that benefit is dramatic. Second, the methods for genetic testing for BRCA1 would have to be developed and refined considerably to reduce the rate of false-positives. Such false-positives raise major ethical and legal questions. Third, once carriers are identified, their continued participation in the trial becomes questionable.

Ethical, Psychosocial, and Legal Issues

The ethical, psychosocial, and legal issues that will arise in these studies are profound and were discussed in another breakout session devoted to this topic. Each of the above study designs requires informed consent from participants, but there are no clear guidelines outlining the proper use of consent in this setting. Two questions must be answered in the near future.

First, must patients give additional informed consent for the use of archived material collected in studies in which genetic testing was not originally planned? Concerning existing archives, one opinion holds that new informed consent is necessary whenever the investigators have not indicated previously to participants the possibility that samples may be used for purposes other than the original study objectives (1). Concerning the development of new archives, a similar view is that potential participants must be informed that their biological materials will be stored for years and that their specimens may subsequently be reanalyzed for currently undetermined research purposes (2).

Second, what is the responsibility of the investigator to notify study participants if genetic testing indicates the presence of a genetic abnormality that confers increased cancer risk? Related questions would be: Should notification depend on the amount of increased risk or on the availability of an intervention? Should assembly-line genetic testing of large DNA banks be discouraged in light of the large numbers of false-positives that are likely to emerge from such routine mass testing?

The current view on this issue is that in obtaining consent for participation in new research, the investigator should indicate exactly what information participants will receive and when this information will be available. That is, the investigator need not be obligated to reveal genetic findings to participants, but his/her plans to withhold such information must be delineated clearly at the outset (3,4). According to the National Advisory Council for Human Genome Research (5), the decision on whether or not to notify participants should depend on the accuracy with which the data and the test predict risk, the efficacy of existing prevention measures, the availability of nondirective education and counseling for family members, and the

likelihood of genetic discrimination with respect to health insurance, life insurance, and employment opportunities.

Further discussion of the ethical and legal issues in predictive genetic testing of cancer-prone individuals can be found elsewhere in this monograph and in the report of a prior National Institutes of Health workshop (6).

Logistical and Feasibility Issues

The study of cancer risk, cancer risk factors, and intervention efficacy in carriers of disease-susceptibility genes is limited in several ways. The most serious limitations arise because of the ethical issues in connection with the high cancer risks of study subjects and their offspring, but there are other logistical issues as well. Since the prevalence of carriers is likely to be small, large, multicenter (and expensive) studies must be mounted. Finally, retrospective cohort studies of cancer incidence following various interventions in high-risk families must avoid the selection bias of counting those cancers that brought the family to attention.

Conclusions

Despite ethical and strategic difficulties, adequately controlled observational and randomized studies will provide the best mechanism for evaluating the types of mutations predisposing individuals to increased cancer risk, the prevalence of these mutations, and the lifetime risks of site-specific cancers borne by carriers of these mutations. The testing of asymptomatic individuals should, at present, be restricted to the research setting. All research protocols should actively recruit ethnic minorities and, when appropriate, members of both sexes to estimate pos-

sible gene-ethnicity and gene-gender interactions. Finally, while the ethical issues associated with these studies present difficult challenges, most of these issues can be anticipated. A working group should be formed as soon as possible by the responsible government agencies to make recommendations for ethical guidelines for the conduct of these studies.

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Notes

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Scale-up Technology: Moving Predictive Tests for Inherited Breast, Ovarian, and Colon Cancers From the Bench to the Bedside and Beyond

Neil A. Holtzman*

The framework for this paper was provided by the breakout session of the same title at the Workshop on Hereditary Breast, Ovarian and Colon Cancer. Scale-up of predictive testing for breast or colon cancer involves the transition between research and standard medical practice—in other words, moving from the bench to the bedside. Several bits of information are needed before the transition can be completed. The information to decide whether testing should be provided to people at high risk of cancer because of family history is more readily obtained than the information to decide whether to offer screening on a population basis.

Testing in High-Risk Families

Once an inherited mutation has been associated with cancer in a family, testing within that family will be informative. Relatives in whom an inherited susceptibility mutation (ISM) is discovered have a high risk of developing cancer (for BRCA alleles, women will be at much higher risk than men), whereas the risk of cancer in those with negative results is lowered to that of people with similar demographic characteristics. If, however, an ISM cannot be identified within a high-risk family, direct testing for mutations will be useless and linkage studies will be needed.

The decision to test routinely depends on the benefits and risks to the asymptomatic individuals being tested. A negative result could reduce anxiety, but a positive test is more problematic. With the exception of interventions in adults found to possess ISMs for familial adenomatous polyposis (FAP), no interventions are of proven benefit in presymptomatic individuals at high risk of other forms of colon or breast cancer (*see below*). (Testing for FAP alleles in children at risk was discussed elsewhere at the workshop.) Uncertainty of the efficacy of interventions could contribute significantly to psychological problems in those with positive test results. Until the effects of interventions are established, the offering of tests in high-risk families should be limited to those willing to participate in trials to establish benefits and risks. An additional problem is third-party reimbursement for testing. In situations in which the risks are high and the benefits are low or unknown, insurers may want access to the results of tests they pay for and might raise premiums, exclude cancer from coverage, or refuse to renew the insurance of people found to be at high risk.

Screening for Genetic Predispositions

The problems of testing in high-risk families also arise in screening, i.e., offering testing to the general population without regard to family history; there are additional problems as well. The deficiencies in our understanding fall in four categories: 1) frequency of the alleles containing ISMs, 2) sensitivity and predictive value of positive test results, 3) efficacy of follow-up interventions, and 4) psychological, educational, and social effects.

Allele Frequency

We do not know how many different alleles confer susceptibility to breast or colon cancer or how frequently each allele occurs. An estimate of collective frequencies could be made by extrapolation from the proportion of all people with breast or colon cancer who are thought to have inherited predispositions. Such an estimate assumes high penetrance of the alleles throughout the population. Anonymously conducted surveys of the population, perhaps using previously obtained specimens containing DNA, could yield direct information on the frequencies of known ISMs. Finding a lower than expected collective frequency suggests that not all ISMs are being detected in the survey; finding a higher frequency suggests either lower penetrance or new mutations.

Sensitivity and Positive Predictive Value

As is the case with most single-gene disorders, genetic heterogeneity seems to be the rule for genes that predispose to cancer. In the 2 months following discovery of the BRCA1 gene, more than 40 mutations have been reported to be associated with cancer. Improvements in DNA hybridization techniques will increase the number of mutations that can be simultaneously detected but will not detect previously unknown alleles, which occur in one or a few families. Before offering tests, the frequency of detectable alleles should be determined (as described above), and estimates should be made of the proportion of the inherited cancer that they represent. To detect all ISMs, tests that assess the function (or functions) of the proteins encoded by cancer genes will be needed. Even if such

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tests were developed in the next 5-10 years, only a small proportion—on the order of 10%—of the specific cancer will occur in people with positive test results. Most breast and colon cancers occur in people without an inherited predisposition; there is no foreseeable way to identify such people before their cancer begins to develop.

The probability that a person with a positive test result will develop cancer (the predictive value of a positive test result [PPV]) will depend on the penetrance of the particular ISM. People with an ISM will not develop cancer until they acquire somatic cell mutations at the same and/or other loci in a single precancerous cell. This will be the case, even when the inherited mutation renders the allele completely expressionless (as with a nonsense mutation in the coding region), although then susceptibility to other mutations may be heightened. Penetrance might be lower in the general population than in high-risk families in which other predisposing genetic or environmental factors, including those that increase the rate of acquired mutations, could be more highly concentrated.

The penetrance of susceptibility-conferring alleles cannot be estimated by anonymous surveys unless it is possible to relate their presence to the presence, or absence, of a specific cancer from records from which all identifiers have been removed. Alternatively, permission may be sought from patients with cancer and age-matched or older controls to assay for ISMs. Finding ISMs in healthy people who are beyond the age at which hereditary cancer usually occurs suggests incomplete penetrance or diminished expressivity. A more costly way to study penetrance is through prospective studies in which people without cancer are tested for ISMs and those in whom they are found are followed until they develop cancer or are beyond the age at which their particular ISMs usually manifest. As part of such studies, environmental factors, including exposure to mutagens and diet, which might influence penetrance, can be examined.

Some have challenged the broad definitions of sensitivity and PPV implied in this discussion. Admittedly, tests that detect ISMs at the DNA level are capable of having perfect analytical sensitivity, at least when performed in high-quality laboratories. But for the person who has a negative result and goes on to get cancer, this analytical excellence is not very comforting. Similarly, if there was a confirmatory test that could indicate which people with an analytically accurate positive test would go on to get cancer, we would not be so concerned about tests with low PPVs. Unfortunately, no such test exists; PPV for the individual is determined only by the future occurrence of cancer.

Efficacy of Follow-up Interventions

Interventions fall into two categories: 1) monitoring for early signs of tumor (by, for instance, colonoscopy or mammography); and 2) prophylaxis, such as Sulindac in those found by testing to be at high risk of developing FAP, or prophylactic colectomy in those at high risk of developing FAP or hereditary nonpolyposis colon cancer (HNPCC), or bilateral mastectomy or chemoprophylaxis in those at high risk of developing breast cancer. Invasive procedures carry some risk. In addition, the low-dose radiation involved in mammography could be more

dangerous to women with inherited predispositions to breast cancer because it increases the chance of somatic mutations. The efficacy of prophylactic mastectomy in women with inherited BRCA mutations has not been established. Moreover, we would not want to use potentially risky and costly interventions in all those discovered by screening to have an ISM until being confident that penetrance of the allele is high. As far as is known today, only alleles for FAP approach complete penetrance. The efficacy of prophylactic interventions in adults found to have FAP alleles, particularly when premalignant polyps are detected, has been better established than interventions in those found to have HNPCC alleles or in women with BRCA alleles.

Psychological, Educational, and Social Effects

As discussed elsewhere at this workshop, many questions of people's reactions to both positive and negative test results remain unanswered. People in the general population may react differently to genetic testing in terms of interest in having the test and responses to test results. If health care insurers were able to raise premiums or exclude cancer from coverage on the basis of test results, people might be deterred from having tests unless third-party payers did not have access to results or could not use them in underwriting. If such were the case, or because of the cost, insurers could refuse to reimburse for predictive testing, denying some patients with insurance access to testing. High costs would put predictive testing out of reach for people without insurance.

The public should be made aware that a negative result for a genetic predisposition does not eliminate the chance of cancer. People with negative tests may acquire a false sense of security and fail to recognize their residual risks. Consequently, they might disregard activities that will reduce risks and facilitate early detection. More research is needed on how to educate and counsel the public so they understand the benefits and limitations of testing.

Are We Ready for Scale-up?

Current testing technologies cannot adequately or accurately handle the large volume of testing that might be demanded if testing for inherited predispositions to common cancers becomes the standard of care. Moreover, until functional assays that can detect faulty expression of a wide array of susceptibility conferring alleles are available, it is likely that many people who harbor ISMs would be missed.

With the possible exception of testing of adults at high risk of developing FAP, for which a functional assay exists, predictive testing in the United States at this time should be conducted under investigative protocols, regardless of whether a person initiated a request for testing or was offered testing. Within high-risk families, questions remain about the safety and efficacy of post-test interventions and the psychological and social impact of testing. Before offering testing to the general population, more information is needed on allele frequencies, which could be obtained from anonymous surveys, and on penetrance, which could be obtained from registries and case-control and prospective studies. Data on safety and efficacy of follow-up interven-

tions could be obtained by clinical trials. Pilot studies, in which testing is offered in return for the participants' willingness to complete questionnaires and interviews, could be used to assess interest in testing, reactions to test results, and the effectiveness of education and counseling modalities. Systematic (investigational) tracing of outcomes should be part of an evolving standard of providing these tests.

It may take considerable time to obtain all of the requisite information. If preliminary data indicate short-term safety and efficacy and pilot studies have recruited a sufficient number of subjects to answer long-term questions, testing might be offered on request with the proviso that definitive statements cannot be made about the benefits and risks of testing. On the other hand, as more information is obtained, it may turn out that the costs and hazards exceed the benefits of routinely offering screening.

We can draw some conclusions from the preceding discussion about when testing for genetic predispositions to cancer could become a standard of care. The tests should be capable of picking up most ISMs for the inherited cancer. The chance that people who test positive for an ISM will develop cancer should be known, as should the ability of follow-up interventions to improve outcome, including survival, through early detection or prophylaxis. Testing under routine conditions should result in minimal psychological harm. Material explaining testing should be demonstrated to provide potential screenees with an adequate understanding of benefits and limitations so their informed consent can be obtained. Finally, health care insurers should not be able to use test results to modify health care coverage.

Despite the many gaps in our understanding of the safety and effectiveness of genetic testing for cancer predispositions, some biotechnology companies are offering tests outside of research protocols. To make matters worse, the provisions of the Clinical Laboratory Improvement Amendments of 1988 for assuring the

quality of clinical laboratory tests have not yet been applied to tests for genetic predispositions; this application does not have a high priority in the agencies implementing the amendments. Moreover, the use of probes and other reagents, which are made in these laboratories or purchased from other sources, have not often received Food and Drug Administration (FDA) approval and seldom follow FDA regulations covering investigational use. Investigational use must be conducted under an institutional review board-approved protocol with informed consent. The FDA has not enforced these requirements. Another major concern is the inadequacy of the interpretation of test results by laboratories, particularly when many nongeneticist providers, who will increasingly be the ones to order these tests, do not have adequate backgrounds in genetics to interpret the results adequately.

In the transition period between research and routine offering of predictive tests, the question arises whether physicians who do not offer such tests could be liable to malpractice suits if the tests were commercially available. Recently published statements by the National Advisory Council for Human Genome Research (1) and the American Society of Human Genetics (2), indicating that testing should not be conducted outside of an investigational environment, afford some protection to physicians and forestall the wide, premature adoption of such tests. Similar statements from oncologists would re-inforce the investigative nature of testing for genetic predispositions to cancer.

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Developing Strategies for Intervention and Prevention in Hereditary Breast Cancer

Barbara L. Weber, Ruthann M. Giusti, Edison T. Liu*

Prophylactic mastectomy, intensified breast cancer screening, and the use of chemopreventive agents have all been recommended to reduce breast cancer risk in women with a family history of breast cancer. Yet, little is currently known about the efficacy of these approaches in reducing breast cancer mortality. The recent identification of BRCA1 and the localization of BRCA2 lend urgency to the need to assess breast cancer intervention and prevention strategies for women likely to carry germline mutations at these loci. At present, families with a history consistent with a BRCA1 or BRCA2 mutation should be tested within the confines of a research protocol and encouraged to participate in intervention and prevention trials. Both retrospective studies and prospective clinical trials are critically needed. While randomized clinical trials would be the optimal mechanism to assess the relative efficacy of these potential interventions, no consensus was obtained as to whether such a trial would be feasible because of strong patient preference for intervention type. It is likely that optimal intervention and prevention strategies will consist of a combined approach to risk reduction. Participants must be appropriately informed of the potential risks as well as the potential benefits of such testing. The potential risks of testing for genetic susceptibility include not only potential psychosocial harm that may result from learning one's carrier status, but also the potential for altered family relationships and insurance and job discrimination. Participants and their family members must be counseled concerning the implication of their test results. [Monogr Natl Cancer Inst 17:99-102, 1995]

The recent identification of the breast cancer susceptibility gene, BRCA1, and the chromosomal localization of a second susceptibility gene, BRCA2, provide a means of assessing risk of breast cancer with a high degree of accuracy based on DNA testing in individuals with mutations at these sites. The ability to identify family members at high risk of developing breast and/or ovarian cancers, and a better understanding of the molecular mechanisms that place these individuals at high risk will likely allow the development of targeted strategies for treatment, prevention, and early detection. However, the growing number of susceptibility genes associated with breast cancer risk (including BRCA1, BRCA2, p53, and the gene for ataxia telangiectasia) and the growing number of unique mutations associated with BRCA1 suggest that hereditary breast cancer represents a heterogeneous group of disorders. Disappointingly, mutant alleles found in families with hereditary breast cancer re-

lated to the presence of BRCA1 have not yet been consistently found in tumors derived from women with sporadic breast cancer (1).

Data from women from families with multiple affected family members suggest a high likelihood of breast cancer in women with a mutant BRCA1 allele. In 33 families with linkage to BRCA1 studied through the Breast Cancer Linkage Consortium (2), it was estimated that by age 70, the cumulative risk of breast cancer among gene carriers was 87%. The cumulative risk of ovarian cancer among women who have had breast cancer was estimated to be 63%. Excess risks of colon and prostate cancers were also observed. Thus, at least for individuals with mutations in BRCA1, developing strategies for reduction of breast cancer risk must be seen in the larger context of cancer risk reduction. These individuals and their potentially affected family members must be counseled concerning risk of other cancers.

A commercially available genetic screening test for mutations at the BRCA1 gene locus could be available within 1 or 2 years. In the face of growing public interest in predictive testing and mounting pressures to commercialize the genetic tests currently under development, the American Society of Human Genetics (3) and the National Advisory Council for Human Genome Research (4) have advocated that, at present, use of these susceptibility tests be restricted to the research setting. The National Breast Cancer Coalition (5) has similarly advocated restraint. In addition, the Department of Health and Human Services National Action Plan on Breast Cancer identified genetic susceptibility as one of its priorities for study. The foremost concern is that the development of a commercially available test for hereditary breast cancer will precede an understanding of how to use test results. Concerns were raised that a genetic test for cancer will be widely used before its sensitivity, specificity, and predictive value in the screening setting can be assessed; before the full implications of a positive (or negative) test are understood; before appropriate clinical strategies for screening, prevention, prophylaxis, or treatment of subsequent cancers are developed and tested; before the psychosocial impact of testing is understood and appropriate procedures for pre- and post-test counsel-

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ing are in place; and before legal safeguards are in place to prevent employment discrimination and loss of insurability. These concerns have been echoed in other sections of this monograph.

This paper summarizes the discussion that took place during the breakout session entitled "Developing Prevention/Intervention Strategies in Hereditary Breast Cancer," held as part of the Workshop on Hereditary Breast, Ovarian and Colon Cancer. Based on current knowledge, participants felt that the development of guidelines for women identified as high risk through testing for genetic susceptibility or through assessment of pedigree data was premature. Rather, this session served to articulate issues and concerns related to the development of clinical trials necessary to provide data concerning the safety and efficacy of intervention strategies in these women.

Approach to Intervention and Prevention Studies in Hereditary Breast Cancer

In discussing prevention/intervention studies in hereditary breast cancer, it is important to note the small number of families that have, to date, had access to genetic testing. It is likely that in the short term, the ability to test for specific mutations in BRCA1 and other identifiable germline mutations affecting breast cancer susceptibility within a given family will be limited to a small number of research laboratories. Thus, most women at risk will continue to be identified on the basis of a strong family history. It was recommended that both groups of women be prospectively recruited for studies to assess the efficacy of the intervention/prevention strategies described below. These two groups should be stratified so as to minimize heterogeneity of the study population.

Session participants outlined a need for both prospective and retrospective studies to be conducted. Prospective identification of susceptible individuals would be required to assess the efficacy of intervention and prevention strategies, to identify potential biomarkers that could serve as intermediate markers of disease progression, and to assess minimally invasive techniques, such as nipple aspiration, core-needle biopsy, and needle aspiration, for the assay of such biomarkers. Retrospective investigation of participants previously enrolled in treatment or prevention trials, tumor registries, and specimen repository programs provides a unique opportunity to use existing resources to study the biology of hereditary cancer in affected women and to assess prognostic factors and treatment outcomes. Retrospective studies would also serve as a potential mechanism to identify family members at risk of hereditary breast cancer; however, in most cases, detailed pedigree data are not currently available from these sources. The genetic testing of retrospectively collected archival materials, a procedure for which informed consent was in most cases not initially obtained and that may have consequences extending beyond the original participant to other potentially affected family members, presents an ethical dilemma as well as a logistical barrier to use of these resources. The development of guidelines within the research community for the ethical use of such archival materials would facilitate research and provide a standard for the protection of human subjects. In both prospective and retrospective studies, careful thought should be given to obtaining appropriate in-

formed consent from study participants identified on the basis of family history for genetic testing of biological materials. Such counseling should include a full discussion of the potential benefits and the potential risks of genetic testing, including the potential impact of such testing on other family members. However, a major concern expressed during the workshop was that individuals who participate in studies that involve testing for cancer susceptibility cannot be adequately protected from loss of insurability and potentially from job discrimination, and patients must be appropriately counseled concerning these risks in the informed consent process.

Potential Interventions

Three general approaches to the development of intervention and prevention strategies have been proposed: prophylactic mastectomy, intensified screening, and chemoprevention. Discussions concerning these approaches are summarized below. The role of lifestyle modifications, such as increased physical activity and reduced dietary fat as potential mechanisms for risk reduction in hereditary breast cancer, were not specifically addressed. The variable age at onset of hereditary breast cancer and the fact that at least some susceptible individuals do not develop breast cancer have led some to postulate that host and/or environmental interactions may modify the expression of this trait. Thus, assessment of the efficacy of such lifestyle modifications, especially in high-risk preadolescent and adolescent girls, may be warranted.

Prophylactic Mastectomy

Bilateral prophylactic mastectomies have been offered to women at risk of hereditary breast cancer because it is widely presumed that prophylactic mastectomy is the most effective way to reduce breast cancer risk. In the absence of linkage or genetic studies to identify a susceptibility marker with a high-risk family, some unnecessary procedures are undoubtedly done in family members who have not inherited a susceptibility allele. Moreover, until the risk associated with individual mutations of BRCA1 is clarified, in the absence of an informative pedigree, some unnecessary procedures may still be done on the basis of mutation testing alone. Currently, little data are now available to assess the efficacy of prophylactic mastectomy. Review of the small number of existing prophylactic mastectomy studies suggests a rate of breast cancer from 1% to 19% (6). Interpretation of these studies is complicated by the heterogeneity of women enrolled in these studies. Ductal carcinoma in situ, lobular carcinoma in situ, contralateral breast cancer, or benign breast disease with atypia were also considered indications for prophylactic mastectomy. Since these factors impart a lower risk of subsequent breast cancer, the reported studies underestimate the risk of breast cancer following prophylactic mastectomy among women likely to carry a BRCA1 germline mutation. Subcutaneous mastectomy has been the most common surgical procedure in this setting; however, it is clear that even the more aggressive Halsted radical approaches leave breast tissue behind (7). There are several case reports of the development of breast cancer following simple mastectomy (in one case, 18 years after simple mastectomy)

(6,8). A study of the effectiveness of prophylactic mastectomy in C₃H mice (9) argues against the notion that risk reduction is proportional to the amount of breast tissue resected. In fact, these investigators speculate that increased prolactin levels following breast resection may paradoxically result in the stimulation of remaining breast tissue and increased breast cancer risk.

While the need for additional data concerning the efficacy of prophylactic mastectomy was universally acknowledged, participants were divided as to whether a trial in which women were randomly assigned to receive prophylactic mastectomy versus intensive screening or chemoprevention was ethical. Even if it was assumed that such a trial was ethical, several participants expressed concerns about the feasibility of conducting a trial that would randomly assign women to a prophylactic mastectomy arm. One key question is how women who are at risk of hereditary breast cancer, the potential participants in such a trial, would view this choice.

It was recommended that, short of a randomized clinical trial, data be collected prospectively on outcomes in women choosing this option. Registry data should include a detailed description of risk factors, extended family history, and information about surgical procedure to permit assessment of the additional risk reduction (if any) of more complete dissection of breast tissue from the skin flap and axilla over standard total mastectomy. Subcutaneous mastectomy is not recommended. For women choosing prophylactic mastectomy, as with other treatment options, quality-of-life assessment should also be incorporated as an outcome measure.

Screening and Early Detection

At present, some investigators recommend that BRCA1 mutation carriers undergo regular mammography screening beginning at age 25 (10). While hereditary breast cancer disproportionately affects younger women, it is clear that conventional film mammography and possibly breast physical examination are less effective in this age group than in older women. It is not known if screening with conventional film mammography would result in decreased mortality from breast cancer in an identified group of younger women shown either to be BRCA1-mutation carriers or to be at increased risk on the basis of family history. Similarly, the potential risk of exposure to low-dose ionizing radiation from routine mammography starting at a young age is unknown. On the basis of observational studies of women exposed to higher doses of therapeutic radiation (therapeutic chest radiation) and among atomic bomb survivors, one might predict that risk of exposure would be greatest among young women in their late teens and early 20s with no prior full-term pregnancy.

The development of more effective technologies for breast imaging is most likely to benefit women at risk of hereditary breast cancer, both because of the increased resolution of lesions within dense breast tissue that could be achieved and also because of the increased likelihood that abnormalities detected in this group represent malignancy. In the short run, digital imaging systems may be the most practical for development and use in large-scale screening programs. Other nonionizing technologies, such as magnetic resonance imaging, positron emission tomography, and ultrasound, also need to be tested among these women, and while unlikely to be justified in large-scale popula-

tion screening programs, may be justified in high-risk women. Correlative studies (some now under way) are clearly needed to assess the efficacy of these techniques. Imaging studies linked to careful pathologic confirmation in women opting to undergo prophylactic mastectomy would be exceedingly useful in assessing new technologies. Additionally, screening studies to assess optimal intervals for conventional mammography or to assess other breast-imaging technologies should incorporate prospective target tissue analysis to define intermediate end points of cancer development.

Chemoprevention

The study of agents with the potential to modulate expression of breast cancer risk is in its infancy. Tamoxifen is the most widely studied chemopreventive agent. Tamoxifen exerts both antiestrogenic and partial estrogenic effects. Tamoxifen exerts partial estrogenic effects on some tissues, including the endometrium. The antiestrogenic effects appear to be mediated through at least two mechanisms. Tamoxifen binds directly to the estrogen receptor, resulting in a conformational change of the receptor, altered RNA transcription, and decreased cell proliferation. Tamoxifen also appears to modulate the production of several polypeptide growth factors. Tamoxifen inhibits estrogen-dependent secretion of transforming growth factor- α (TGF- α) and epidermal growth factor and stimulates production of transforming growth factor- β (TGF- β). Both TGF- α and epidermal growth factor bind to cell membrane receptors and promote breast cancer cell proliferation. TGF- β inhibits the growth of many epithelial cell lines, including estrogen receptor-negative breast cancer cells (11,12).

On the basis of the clear demonstration of reduction in occurrence in second primary breast cancers in the contralateral breasts of postmenopausal women receiving tamoxifen, the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial was undertaken (13). This randomized, double-blind, placebo-controlled clinical trial of tamoxifen use for primary prevention of breast cancer currently enrolls premenopausal women with an increased risk of breast cancer equivalent to that of a 60-year-old woman, based on the model by Gail et al. (14). It is estimated that a small minority of the 16 000 women to be recruited for this trial would likely be at risk for hereditary breast cancer. Concerns about long-term toxicity and the lack of a clear benefit demonstrated to date in premenopausal women has made the recruitment of premenopausal women to this trial intensely controversial (15).

The retinoids, including vitamin A and its synthetic derivatives, have been widely studied in preclinical models. An early study (16) has suggested a prevention of cancer or cancer recurrence at several sites. The retinoids bind to retinoic acid receptors and retinoid X receptors and act as transcription factors binding to multiple target genes. One such target gene, TGF- β , has an antiproliferative effect on breast epithelium (17).

The synthetic retinoid 4-hydroxyphenyl retinamide (4-HPR or fenretinide) has been used as a chemopreventive agent in breast cancer. Based on preclinical data that suggests synergism between tamoxifen and 4-HPR, more than 3000 women with early-stage (T_{1,2}N₀) have been enrolled in an ongoing large-scale, placebo-controlled Italian trial of 4-HPR alone or tamox-

ifen and 4-HPR for prevention of contralateral breast cancer. This combination is currently being evaluated in an adjuvant study in postmenopausal node-positive women in an Eastern Cooperative Oncology Group phase III trial. A pilot chemoprevention study of tamoxifen and 4-HPR for primary prevention of breast cancer in high-risk women has recently been undertaken at the National Cancer Institute. This study, while too small to assess efficacy, is aimed primarily at identification of biomarkers of tamoxifen-4-HPR effect and identification of intermediate end points that may precede the development of breast cancer.

Participants agreed that there are currently no data on which to assess the efficacy of chemopreventive agents in the primary or secondary prevention of breast cancer in women at high risk of hereditary breast cancer. Such studies are clearly needed and should incorporate assessment of biomarkers and intermediate end points. Optimally, such agents should be selected based on an understanding of the biologic defects in women being enrolled in prevention studies.

Conclusion

The recent identification of BRCA1 and the localization of BRCA2 lend urgency to the need to develop strategies for intervention and prevention of hereditary breast cancer and to make these options available to women at risk. To provide women and their potentially affected family members with sufficient data to make a truly informed decision concerning breast cancer risk, risk reduction, and cancer treatment, the spectrum of BRCA1 and BRCA2 mutations and the implication of these mutations for cancer risk must be better understood. The efficacy of prophylactic mastectomy, a frequently recommended risk-reduction strategy, must be defined. The natural history and clinical characteristics of hereditary breast cancer that will ultimately determine the potential use of intermediate end points and the efficacy of early detection and chemoprevention must also be clarified. Participants in clinical trials for intervention and prevention of breast cancer risk must be appropriately counseled concerning both the potential benefits and the potential risks that may result from their decision to agree to genetic testing. These risks include not only the psychosocial impact of determining carrier status but also the very real risk of loss of insurability and job discrimination. While safeguards to adequately protect participants from these risks are clearly needed, they do not cur-

rently exist. As with other studies involving testing for genetic susceptibility, workshop participants recommended that assessment of intervention and prevention strategies should be conducted in the context of a clinical trial by a multidisciplinary research team to ensure the appropriate and ongoing counseling of participants.

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Developing Intervention/Prevention Strategies for Individuals at High Risk of Developing Hereditary Ovarian Cancer

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In 1994, an estimated 24 000 new cases of ovarian cancer will be diagnosed in the United States. Most of these patients will have disease spread beyond the ovary at the time of diagnosis; despite tumor debulking and aggressive platinum-based chemotherapy, their long-term prognosis is poor. In view of the advanced stage of disease at the time of diagnosis and the poor results of conventional therapy, advances in early detection and/or prevention are desperately needed. The recent recognition that a family history of the disease is perhaps the strongest risk factor for the development of ovarian cancer offers a unique opportunity to identify women at high risk for ovarian cancer and to develop effective screening methods and prevention/intervention strategies for these high-risk women. The results of the breakout session "Developing Strategies for Intervention/Prevention Trials for Individuals at Risk of Hereditary Ovarian Cancer" are summarized here. The majority of the discussion in this session focused on three major issues: 1) identification of moderate- and high-risk individuals who would potentially benefit from screening, prevention, and intervention efforts; 2) assessment of the effectiveness of current screening modalities and the usefulness of current intervention/prevention strategies; and 3) recommendations for clinical trial design. [Monogr Natl Cancer Inst 17:103-106, 1995]

In 1994, an estimated 24 000 new cases of ovarian cancer will be diagnosed in the United States. The majority of these patients will have disease spread beyond the ovary at the time of diagnosis; despite tumor debulking and aggressive platinum-based chemotherapy, the long-term prognosis for these patients is poor. In view of the advanced stage of disease at the time of diagnosis and the poor results of conventional therapy, advances in early detection and/or prevention are desperately needed if a significant impact on mortality from this disease is to be made in the near future. The recent recognition that a family history of the disease is perhaps the strongest risk factor for the development of ovarian cancer offers a unique opportunity not only to identify women at high risk of developing ovarian cancer but also to develop effective screening methods and prevention/intervention strategies for these high-risk women.

The following is a summary of the discussion at the breakout session "Developing Strategies for Intervention/Prevention Trials for Individuals at Risk of Hereditary Ovarian Cancer," which

was part of the National Cancer Institute (NCI) Workshop on Hereditary Breast, Ovarian, and Colon Cancer, held April 26-27, 1994. The charge to this breakout session was to develop intervention and prevention strategies for women at high risk for the development of hereditary ovarian carcinoma.

Identification of the Moderate- or High-Risk Individual

Three distinct types of hereditary ovarian cancer syndromes have been identified to date. These include the breast-ovarian syndrome, hereditary nonpolyposis colon cancer, and the least common site-specific ovarian cancer family syndrome. In these families, predisposition to cancer is inherited as an autosomal dominant trait, and transmission occurs through either the maternal or the paternal parent. According to mendelian genetics, the children of an affected woman have a 50% chance of inheriting the predisposing mutation. The first susceptibility gene for breast-ovarian cancer, known as BRCA1, has been localized to the long arm of chromosome 17 (1). BRCA1 appears to be responsible for at least 80% of breast-ovarian and a similar proportion of site-specific ovarian cancer families (1,2). In breast-ovarian cancer families, the cumulative risk for breast or ovarian cancer in women with a mutant BRCA1 allele was estimated to be 67% by age 50 and 76% by age 70, indicating that BRCA1 is a highly penetrant predisposing gene for both malignancies. BRCA1, which has just recently been identified, is a large gene consisting of 21 exons scattered over 100 kilobases of genomic DNA with germline mutations identified in five of eight breast and breast-ovarian cancer kindreds (3,4).

Although BRCA1 had not been cloned at the time of this workshop, a number of issues were identified that needed to be addressed once the gene was cloned. First, the spectrum of mutations needs to be described, and a reliable clinical test with no false-positives will need to be developed. Second, better estimates of the lifetime risk of cancer associated with BRCA1 mutations need to be determined. Although it is thought that a

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woman who carries a defective BRCA1 allele has a 76% chance of developing cancer by age 70, these data are based on very large families with multiple affected members and may actually overestimate ovarian cancer risk. In addition, specific BRCA1 mutations may have different penetrance and may predispose women to different types of cancer. Moreover, because not all women with germline BRCA1 mutations develop cancer in their lifetime, environmental or reproductive factors may be able to prevent the tumorigenic action of a mutant BRCA1 allele. Also, the contribution of germline mutations in BRCA1 to small family clusters and apparently sporadic ovarian cancer cases is unknown. Such information is essential in assessing the percentage of cancer cases due to genetic factors. Finally, the psychosocial impact and legal ramifications of risk assessment and mutation analysis, including potential loss of health and life insurance, are uncharted territories. Until these issues are addressed, it was believed that mutation analysis when available should be performed only in carefully controlled research settings.

Until a reliable test is available for germline mutations in BRCA1 and other potentially predisposing genes, family history is the most reliable predictor of ovarian cancer risk. The consensus of the group was that first- and second-degree relatives of an affected individual from an autosomal dominant breast-ovarian or site-specific ovarian cancer families should be considered the truly high risk group for ovarian cancer. Although only 1% of women with ovarian cancer have a family history consistent with an autosomal dominant mode of transmission, an additional 7% have a family history of at least one affected first- or second-degree relative. Assessment of risk in these individuals is more difficult. Compared with the lifetime risk of ovarian cancer in the general population of 1.4%, the risk for women with a single affected first-degree relative is increased to 5%; in women with two affected first-degree relatives, it is increased to 7% (5). Because of this threefold to fivefold excess in ovarian cancer risk in women with a positive family history, it was the consensus of the group that these women should be considered a moderate-risk group. The optimal method to assess family history and to assign risk is unknown. It was of concern that obtaining extended, well-documented family histories is time-consuming and may not be performed by the primary caregiver. Effective methods to obtain such a history and reliable risk assessment models need to be developed.

Conclusions

1) Until a reliable test for germline BRCA1 mutations is developed, women who are first- or second-degree relatives of an affected member of an identifiable autosomal dominant ovarian cancer family (breast-ovarian, site-specific ovarian) should be considered at high risk for ovarian cancer.

2) Women with one or more relatives with ovarian cancer without firm evidence of an autosomal dominant mode of transmission should be considered at moderate risk for the disease.

3) Because of an increased incidence of ovarian cancer in individuals in the moderate- and high-risk categories, they are the optimal group in which to assess the impact of screening and prevention/intervention strategies.

4) The true penetrance of BRCA1 mutations and its contribution to ovarian cancer in the general population are unknown.

Recommendations

1) Optimal methods for obtaining accurate, extended-family medical histories and accurate risk assessment need to be ascertained.

2) Reliable tests for detecting BRCA1 mutations need to be developed.

3) The precise cancer risk, including type and penetrance, associated with specific germline BRCA1 mutations needs to be ascertained.

4) The psychosocial impact and legal ramifications of risk assessment and mutation testing need to be ascertained in the moderate- and high-risk groups.

5) The prevalence of predisposing mutations needs to be determined in the general population and in a large cohort of consecutive ovarian cancer patients in order to ascertain the contribution of germline mutations to ovarian cancer in the general population. This goal would best be accomplished utilizing the resources of national cooperative groups.

Assessment of the Effectiveness of Current Screening Modalities and Prevention/Intervention Strategies

Current screening modalities potentially useful in the surveillance of women at moderate to high risk for ovarian cancer include transvaginal ultrasound and serum CA-125 determinations. Transvaginal ultrasound provides an accurate morphologic image of the ovary and has been proven to be safe and well tolerated by patients (6). Large-scale screening studies in the general population and in women with a family history of the disease indicate that transvaginal ultrasound is extremely sensitive in the detection of small, asymptomatic, potentially curable early-stage tumors (6,7). Bourne et al. (7), for example, in a screening study of more than 700 women with a first- or a second-degree relative with ovarian cancer, detected three cases of ovarian cancer by transvaginal ultrasound. All of these cases were stage IA, and none of the women in this series developed ovarian cancer within the 1st year of the scan (7). Although there are no randomized, prospective clinical trials of transvaginal ultrasound screening, these data would suggest that such screening is a very sensitive procedure for the detection of early-stage ovarian cancer. However, the transvaginal ultrasound is limited by its inability to differentiate benign from malignant tumors, particularly in premenopausal women, and it was of concern to the group that the high false-positive rate may lead to unnecessary surgical intervention.

Of the tumor markers available, CA-125 is the serum marker used most extensively in ovarian screening trials. However, because serum levels are directly related to tumor volume, small, potentially curable, early-stage tumors may not be detected by this technique. In fact, only 50% of clinically detectable stage I ovarian tumors and a much smaller percentage of ovarian malignancies detected by transvaginal ultrasound have elevated CA-125 levels, thus limiting its sensitivity in detecting small, potentially curable ovarian cancers (6,8). Moreover, as with transvaginal ultrasound, the high rate of falsely elevated serum levels associated with benign disease may lead to unnecessary intervention.

It was the consensus of the group that transvaginal ultrasound provides the optimum current ovarian screening method, but studies demonstrating its effectiveness have been limited by the relatively low prevalence of the disease in the general population and the lack of any randomized, prospective screening trials. Despite these limitations, it was noted that the NCI Consensus Statement on Ovarian Cancer recommended annual screening with serum CA-125 and transvaginal ultrasound in women with a family history of ovarian cancer.

It was noted that both pregnancy and oral contraceptive use have been shown to offer considerable protection against ovarian cancer. According to the Cancer and Steroid Hormone Study of the Centers for Disease Control and Prevention, the relative risk for ovarian cancer decreased to 0.6 in women who used oral contraceptives for a minimum of 3 months and to 0.4 in women after more than 5 years of use (9). In this study, the protective effect of oral contraceptives was still evident as long as 10 years after discontinuation of use. More recently, tubal ligation and, to a lesser extent, hysterectomy have also been shown to be inversely related to ovarian cancer risk in the general population (10). After adjustment for age, oral contraceptive use, and parity, the relative risk for ovarian cancer was 0.33 following tubal ligation and 0.67 after simple hysterectomy. For these reasons, oral contraceptives and tubal ligation may provide a useful prevention strategy in women at moderate to high risk of developing ovarian cancer. However, it was noted that there are no data that specifically address the protective effect of oral contraceptives or tubal ligation in the management of women with a known predisposing mutation. These factors may not influence risk in women with highly penetrant germline mutations. For this reason, epidemiologic studies addressing the impact of these factors on ovarian cancer risk in the truly high risk women are needed before these modifiable risk factors are widely accepted as effective prevention strategies. Genetic epidemiology studies of environmental and reproductive factors on ovarian cancer risk in affected and unaffected gene carriers should provide useful information.

Prophylactic removal of the ovaries is commonly offered to women with a moderate to high risk of developing ovarian cancer. It was the consensus of the group that, because of the current inability to detect ovarian cancer in a preinvasive state and the absence of a reliable genetic marker, this procedure should be strongly considered in women who are members of an autosomal dominant ovarian cancer family. It was of major concern to the group that knowledge regarding the effectiveness of prophylactic oophorectomy is limited. The occurrence of peritoneal carcinomatosis clinically and histologically identical to ovarian cancer following prophylactic oophorectomy is well documented (11,12). Moreover, there are no reliable data regarding the specific surgical procedure needed, i.e., laparoscopy versus laparotomy, the need for concomitant removal of the uterus and tubes, and the psychosocial impact of prophylactic removal of the ovaries. When prophylactic oophorectomy was initially described, it was recommended that it be done through a midline incision, with total abdominal hysterectomy, bilateral salpingo-oophorectomy, washings, and lymph node and omental biopsies. This procedure now is commonly done by simple laparoscopic removal of both ovaries, leaving in place the uterus.

Finally, the risk-benefit ratio in patients at moderate risk of developing ovarian cancer was unclear. The morbidity and mortality associated with surgical intervention, castration, and hormone replacement therapy may or may not be justified in these women.

Conclusions

- 1) Transvaginal ultrasound is highly effective in detecting asymptomatic, potentially curable, early-stage ovarian cancers.
- 2) Serum CA-125 determinations have limited sensitivity for small-volume ovarian cancers.
- 3) The usefulness of oral contraceptives or tubal ligation in the prevention of ovarian cancer in women with a genetic predisposition to the disease is unknown.
- 4) Prophylactic oophorectomy appears to be warranted in the truly high risk group, particularly in individuals with germline BRCA1 mutations.

Recommendations

- 1) Methods are needed to enhance the specificity of current screening modalities.
- 2) The effectiveness of current screening recommendations should be evaluated in a prospective, randomized fashion in women at increased risk of developing ovarian cancer.
- 3) The effects on risk of environmental and potentially modifiable risk factors, particularly oral contraceptive use and tubal ligation, need to be assessed in the high-risk group, specifically affected and unaffected gene carriers.
- 4) The risks and benefits of prophylactic oophorectomy should be ascertained, and recommendations should be developed for this procedure.

Recommendations for Clinical Trial Design

Currently, because prophylactic oophorectomy is the only method known to prevent the development of ovarian cancer, it was the consensus of the group that this should be offered to truly high risk women, particularly gene carriers. However, it was of concern that the effectiveness of this procedure in preventing the subsequent development of peritoneal carcinomatosis has not been established. As mentioned earlier, the minimum surgical procedure to prevent subsequent peritoneal carcinomatosis is unknown. It was recommended that we seek information regarding prophylactic oophorectomy by an observational study through the NCI, national cooperative groups, or a large consortium. Although retrospective data regarding prophylactic oophorectomy are useful, such a study would ideally be performed prospectively with careful documentation of family history and surgical technique, consent for genetic testing on stored materials, and quality-of-life assessment before and after prophylactic oophorectomy.

It was the consensus of the group that the truly high risk group, i.e., members of autosomal dominant breast-ovarian cancer and site-specific ovarian cancer families and BRCA1 gene carriers, is the optimal group for screening and prevention trials. Although a randomized clinical trial between prophylactic oophorectomy versus screening or prevention measures in high-risk women seems ideal, such a study presents significant ethi-

cal and legal issues. Because prophylactic oophorectomy is the only known way to prevent ovarian cancer in high-risk women, there was considerable concern about randomly assigning these patients to a no-surgery arm. This concern was based on the lack of long-term survival data on women with ovarian cancer detected by transvaginal ultrasound and the lack of data on the interaction between potentially modifiable risk factors, i.e., oral contraceptives and tubal ligation, and ovarian cancer risk in BRCA1 gene carriers. For this reason, retrospective studies of high-risk women and prospective studies of women who do not desire prophylactic oophorectomy were recommended to assess the impact of modifiable risk factors and to analyze the effectiveness of current screening recommendations in high-risk women. An alternative study design in high-risk women would be to allow the patient to choose the arm, i.e., surgery versus screening or prevention. Such a trial would need to be carefully analyzed according to extent of family history and prevalence of BRCA1 mutations to prevent biases. Randomized clinical trials of screening or risk factor modification versus prophylactic oophorectomy were deemed appropriate for a very well defined, moderate-risk group. There was no consensus on the minimum ovarian cancer risk to warrant inclusion in such a trial. It was recommended that all such studies include consent for genetic testing on stored materials, genetic counseling, and quality-of-life assessments as study end points.

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Developing Strategies for Intervention/Prevention Trials of Individuals at Risk of Hereditary Colon Cancer

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Environmental causes are thought to be the etiology of most colorectal cancers (sporadic colorectal cancer). However, about 10% of the cases result from one of two well-defined forms of hereditary colorectal cancer: hereditary non-polyposis colorectal cancer and familial adenomatous polyposis. The development of intervention/prevention strategies for patients with newly diagnosed colon cancer and their families at high risk for hereditary colon cancer was framed in the questions: "Who is the target?" and "How to identify those at high risk"? There is agreement that genetic analysis for hereditary colorectal cancer holds tremendous promise but that it requires the development of highly structured protocols to ensure that genetic testing is a positive experience for patients at high risk. Appropriate strategies to identify high-risk patients would include recruiting minority (ethnic, racial, and socioeconomic) populations into these studies. Implementation of the protocol would begin with primary-care physicians working with cancer prevention centers in a network to achieve informed consent, to obtain bank-blood samples for genotyping, and to provide the social support and genetic counseling necessary to achieve the goal of a positive experience in cancer prevention. Initial studies would be directed at the known hereditary colorectal cancer groups, including familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. [Monogr Natl Cancer Inst 17:107-110, 1995]

Environmental causes are thought to be the etiology of most colorectal cancers (sporadic colorectal cancer) (1). However, about 10% of the cases result from one of two well-defined forms of hereditary colorectal cancer: hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).

HNPCC (or Lynch syndrome) has several cardinal features. First, HNPCC is an autosomal dominant disorder caused by mutation in one of a group of genes involved in DNA nucleotide mismatch repair (2-9). These genes include hMSH2 (human mutS homolog 2) on the short arm of chromosome 2, hMLH1 (human mutS homolog 1) on the short arm of chromosome 3, and hPMS1 and hPMS2 (human postmeiotic segregation 1 and 2) on the long arm of chromosome 2 and the short arm of chromosome 7. Second, colorectal cancer occurs at a young age (on average, 40-50 years of age) compared with sporadic colo-

rectal cancer, which develops in the 7th decade of life (10). Third, colorectal tumors arise primarily (60%-80%) on the right side of the colon (proximal to the splenic flexure); in sporadic colorectal cancer, only 23%-32% of tumors are right sided (10). Fourth, synchronous and metachronous colorectal malignancies can occur (10). Finally, patients and family members are at high risk for endometrial and other cancers.

FAP is the other well-defined form of colorectal cancer. FAP is an autosomal-dominant disease characterized by the development of hundreds of colorectal adenomas in young adults (11). If prophylactic colectomy is not performed, virtually all affected individuals will develop colorectal cancer by the 5th decade of life. Recently, investigators have discovered that FAP is caused by germline mutations of the adenomatous polyposis coli (APC) gene located on the long arm of chromosome 5 in band q21 (12-15). FAP can also be associated with various extracolonic lesions. Benign extraintestinal manifestations include epidermoid cysts, osteomas, occult radio-opaque jaw lesions, pigmented ocular fundus lesions, and desmoids.

Patients with FAP are at increased risk for intestinal cancers, especially duodenal and periampullary carcinomas, and for rectal cancer in those with subtotal colectomy. Extraintestinal cancers reported in association with FAP include tumors of the thyroid gland, adrenal gland, biliary tree, and pancreas (16-19).

Who Should Be the Target of Intervention?

The first question that must be asked when developing individual intervention/prevention strategies for newly diagnosed patients and their families at high risk for hereditary colon cancer (18,19) is "Who should be the target of intervention and how to identify this population?" The answer, of course, depends on the ability to assess risk with sufficiently high sensitivity and specificity to distinguish between high- and low-risk groups. Mutation in four DNA mismatch repair genes (MSH-2, MLH-1, PMS-1, and PMS-2) has been identified as confirming risk for HNPCC (3,7). Hereditary alterations in HNPCC genes in the population at large may be only as frequent as one in 200-400

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but occur in 5%-10% of people with colon cancer. Individuals with these genetic alterations have an estimated 70% lifetime risk of developing colon cancer as well as increased chances of developing cancer of the uterus, ovary, bladder, and other gastrointestinal organs.

Population screening and other approaches to genetic surveillance will need to be cost-effective methods of treatment, and should include identification of additional genes that may also imply dramatic susceptibility to colon and other cancers. Currently, HNPCC genotyping can distinguish with near certainty those individuals who will develop colorectal cancer over their lifetime versus those with a family history but no increased personal risk of the disease. Protocols must be ethical and culturally sensitive to the target populations and conducted as Institutional Review Board (IRB)-approved clinical investigations (20).

Genotyping in HNPCC will likely follow protocols used in FAP. Examination for mutation of the APC gene in individuals at risk for FAP is now an integral part of the clinical management of these families and has dramatically simplified surveillance strategies.

Sample Protocol for Hereditary Family Study

The hereditary family study proposed by Li et al. (21) is an example of HNPCC genotype testing. This protocol would first explain the disease to the index patient with colon cancer (or a concerned first-degree relative). The individual would, in turn, give informed consent to participate and recount his or her personal and family history of cancer. When appropriate, the index case subjects would be asked to permit contact with other family members and to provide a blood sample for genetic analysis. A concerned blood relative would be eligible for the study when a family history of colon cancer is established by three first-degree blood relatives; one individual would be the index patient and at least one would be diagnosed before the age of 50. Other potential index cases would be patients with close relatives with a history of colon cancer before the age of 40, a history of multiple primary cancers in the patient or a close relative, any family group with an interesting cancer history, or any family group with a history of FAP.

Once results of genetic analysis were available, the patient would be informed and would receive genetic and psychologic counseling. Permission to provide the information to the patient's physician would be sought. Recommendations for cancer surveillance, chemoprevention, study participation, and other management issues would then be discussed with the patient and physician in an ongoing fashion (22-25).

Population-Based Research

Another approach to genetic testing involves population-based research investigating groups with a very low incidence of colorectal cancer. This would provide important clusters to compare with existing or new candidate genes for risk assessment (11,18). RER (replication error phenotype) status would also be useful in defining risk. RER-negative patients may not be at risk for hereditary forms of colorectal cancer, whereas those with RER-positive tumors probably are. Other indicators of increased

risk include proximal site of the cancer, age at diagnosis, and environmental and dietary factors. Genetic analysis holds tremendous promise through well-structured protocols to ensure that genetic testing will be a positive experience for patients with a high risk of colorectal cancer. It will not be possible to initiate prevention and treatment programs until these protocols are established using scientific methods (18-21).

Identification of High-Risk Patients

The working group supported evaluating the hereditary status of patients with colorectal cancer and those individuals from high-risk families. However, genotyping based on population screening is premature (22,23). Instead, a blood bank must be initiated to collect and store samples from individuals at high risk for further genotype testing to design population-based screening.

Protocols to study high-risk patients must identify colorectal cancer in minority (ethnic, racial, and socioeconomic) populations and recruit these individuals to join ongoing and new studies. In addition to the standard public relations and public education efforts, recruitment resources will be needed to go into minority communities with peer educators to identify index cases.

Who Should Identify High-Risk Individuals?

The working group concluded that primary-care physicians should be responsible for working in concert with oncologists, gastroenterologists, surgeons, and other allied health professionals to identify these individuals. A protocol to assist these health-care providers to coordinate efforts in identifying and stratifying patients into low- and high-risk groups must be developed. Special prevention billing using (Current Procedural Terminology) codes will be necessary to compensate health-care providers. In addition, physician and health-care provider education is required to implement the stratification procedures.

Specialized Centers

Because most communities will be unable to meet the complex requirements of gene testing, a network among the community health services and specialized test centers must be established. These centers will have the necessary resources to provide counseling, surveillance, and prevention protocols. The test centers will in turn contribute to national registries to facilitate contacting at-risk family members throughout the United States. Indeed, these centers and registries are essential for the successful use of this approach for prevention, early diagnosis, and treatment. Counseling patients about their increased risk of colorectal cancer will be critical. Hotlines staffed by experienced professionals will need to be available to both patients and health-care providers as new data are published in scientific journals (10,18,19).

Strategies for Prevention, Surveillance, and Intervention

Much work remains to be done at the basic scientific level—from probing the dysfunction of the altered genes to designing novel therapies. The first prevention strategy employs a highly structured and thoroughly tested education program to explain the results of genotyping and their relation to cancer risk (21). This approach would be used in the centers described above. The second strategy endorses the use of public health approaches, including nutritional counseling based on the U.S. Dietary Guidelines (26) and National Cancer Institute diet programs emphasizing five-a-day servings of fruits and vegetables (27).

Epidemiologic data (28) support the conduct of dietary trials as chemopreventive agents, particularly when they comply with U.S. Dietary Guidelines and are not toxic. Given the results of recent single-agent approaches (29), these trials should examine multiple nutrients as adjuncts to the U.S. Dietary Guidelines (low-fat, high-fiber, and nutrient-dense) and the U.S. Department of Agriculture Food Pyramid to identify the most effective agents in inhibiting tumor growth and metastases (30).

Recently, Kidd et al. (31) compared diet, concentration of plasma fatty acids, and the proliferative potential of colorectal mucosa in whites and fishermen of mixed race in South Africa. They reported that the fishermen have a higher intake of fish (4 versus 1 oz/day), lower intake of fruit and vegetables (7 versus 12 oz/day), lower intake of calcium (377 versus 662 g/day), and lower intake of fiber (10 versus 17 g/day). Despite the lower intake of “protective” foodstuffs, such as fiber, calcium, and vegetables in the fishermen, biomarkers of cell proliferation (e.g., gene markers Ki67, p53, and TGF- α) and plasma omega-3 fatty acids concentrations were related to decreased proliferative mucosal activity in mixed-race fishermen compared with whites (31). Other chemotherapeutic agents, besides omega-3 fatty acids (32–35), include nonsteroidal anti-inflammatory drugs (36). Other chemopreventive agents include aspirin, folic acid, and calcium.

Colorectal Surveillance

Additional guidelines must define the frequency of endoscopic monitoring as well as the technique (16,17) to effectively implement colorectal surveillance. Periodic updates comparing genotype and phenotype correlations will lead to more sensitive and specific surveillance guidelines. This is especially necessary in those individuals with extracolonic lesions who develop hereditary colorectal cancer.

Experts recommend that women at risk for HNPCC should undergo surveillance for endometrial carcinoma. This includes vacuum curettage of endometrial cells for histopathologic study starting at 25 years of age and then annually. The value of other studies, such as abdominal or transvaginal ultrasound and CA-125, is uncertain.

When at-risk women develop colorectal cancer, some investigators recommend prophylactic total-abdominal hysterectomy and bilateral salpingo-oophorectomy; if these affected women

want additional children, endometrial carcinoma surveillance is intensified to every 6 months.

An example is the model for FAP, another hereditary form of cancer, in which the ability to test genotype has drastically reduced the amount of surveillance required (19). Mutation of the APC gene that causes FAP is detectable by present technology in 80% of families with FAP. Consequently, current protocols test an affected member to determine whether the family gene mutation can be identified. Once the gene mutation is found, all at-risk pedigree members can be gene tested, with 99% confidence in the positive or negative test result. In individuals who test negative for gene mutation, surveillance for FAP is eliminated or sharply curtailed.

With regard to prophylactic surgery, the FAP model should be followed that can be characterized as watchful waiting. Even those individuals who are genotypically positive should wait for evidence of phenotypic expression before colectomies are performed. Of course, as more information is gained from the correlation between genotype and phenotype, these guidelines for HNPCC may change.

Barriers to the Development of Treatment Strategies

A national cooperative trial is necessary to test the validity of treatment strategies to accrue the large sample size. Also, the physical distance between family members and the variance of outcome measures and environmental factors will necessitate a multisite clinical trial. Furthermore, the tumor growth rates of colorectal cancer will affect evaluation of chemoprevention trials that will take several years, even using biomarkers.

In addition, the identification, surveillance, and treatment of high-risk individuals will involve increased costs that need to be appropriately shared by the health-insurance system and research in academic centers. Perhaps unique to colon cancer is that sensitive and specific genotyping allows for the diagnosis and treatment of hereditary cancer. Genotypes identified to date represent only the beginning, and parallel investigations into other genotype abnormalities will also be needed.

Future Considerations

Priority for future research includes developing cost-effective and time-sensitive prevention studies using transgenic mice to identify successful treatment modalities (i.e., dietary changes, aspirins, etc). New predictors of high-risk cohorts from genotypic screening (e.g., individuals with strong family histories and poorly defined linkage) could clarify the role of population screening. The ethical use of hereditary testing requires carefully constructed protocols sensitive to the patient's experience; the type of counseling used in other hereditary screening is needed. Specific guidelines must be developed to ensure participation in the protocol prior to contacting any family member of an index case. Initial studies would be restricted to appropriate IRB-approved research protocols until experience is gained. Knowledge acquired from other hereditary diseases must be incorporated. The priority is to develop comprehensive protocols, a network of specialized centers, and a registry that will most ef-

ficiently provide sites for obtaining samples, counseling, education, and treatment. A distinction must be made between screening and testing, with the current approach characterized as testing. There is consensus that screening of healthy people is premature. Screening carriers of RER-positive tumors perhaps could provide data on which to base future screening initiatives.

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Evaluating Children and Adolescents for Heritable Cancer Risk

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The dramatic success in the identification of genes predisposing to human cancer, including those predisposing to breast, ovarian, and colon cancers, presents new opportunities for and dilemmas about genetic testing. The new opportunities seem to offer almost limitless long-term potential for determining the actual risk associated with these genes; defining the role of other genetic or environmental factors in determining cancer risk; identifying precursor lesions that may reveal the mechanism of carcinogenesis in the general as well as the genetically predisposed population; and developing programs of early detection, prevention, and treatment. However, in the early phase of determining the role of each of these genes in cancer development, the question of the ethics of genetics testing looms large. Who should offer such tests, and on what basis should they be given? How should such decisions be made? These are not only issues for the medical and legal communities and for individual patients and their physicians; the issues come into the public domain, as the identification and cloning of these cancer genes have been major media events, popularized not only among those most likely to benefit from testing but also among the general population, who may want to seize any opportunity for testing for a dreaded disease.

Adults are motivated to be tested by the hope that they will obtain good news or at least that the anxiety of uncertainty will be relieved (1-3). Some also want to have their children tested. There are few data, however, on the impact of genetic testing of children for adult-onset disorders. The charge to this discussion group was to evaluate genetic testing of children in families with a known genetic predisposition to cancers of the breast, ovary, and colon, diseases for which screening and early detection or prophylactic surgical intervention may reduce the morbidity or mortality from those cancers.

To date, committees examining the ethics of genetic testing in the United States (4) and the United Kingdom (2) have made similar recommendations about genetic testing of children, i.e., that "children should generally be tested only for genetic disorders for which there exists an effective curative or preventive treatment that must be instituted early in life to achieve maximum benefit" (4). This follows the traditional medical model that testing is appropriate only if there is a potential medical benefit.

Dr. P. Reilly (this monograph) has presented another perspective for our consideration, a model that not only assesses direct medical benefit to the child but also considers the issue of parental choice or the perception of benefit to the parents in their role as guardians of the child. This approach places more emphasis on the benefit to the family as a unit, as opposed to the

child alone, and has a solid legal precedent in the United States and the United Kingdom as well.

In addition to considering methods of direct medical or indirect familial benefit to the child, Dr. Reilly emphasized primary consideration of the autonomy of the child and recognition that parents may not always make the best choice for their children but will be influenced, consciously or unconsciously, by their own motives. Making the autonomy of the child the principal concern implies that, if there is no immediate medical benefit to testing at a young age, the decision for testing should not be made until the child can actively participate in the decision. Dr. N. A. Holtzman (this monograph) and others (3,4) have suggested that an ombudsman, independent of the parents and the physician or principal investigator, should be appointed to look out for the child's best interest.

Our discussion group has also deliberated on what we perceive are the realities of genetic testing for cancer predisposition in children. We estimated the demand and need for testing of children from the following independent observations:

1) Some parents with a known genetic predisposition to cancer are already pressing for testing of their children. Many investigators and patient advocates at this meeting have reported this.

2) We anticipate that our scientific knowledge will evolve rapidly and will provide medical and biologic bases for genetic testing of and intervention in children. This prediction is based on the following considerations:

(a) The genes for breast (BRCA1) and colon (MSH2, MLH2, PMS1, and PMS2) cancers, which are common cancers, have been identified by studying families with many affected members (5-12). As genetic testing is applied to these and other less highly selected kindreds and penetrance is redefined on the basis of gene-carrier status, important, although perhaps rare, manifestations in childhood may become apparent. An example is familial adenomatous polyposis, which is due to mutation at the APC locus. While the major manifestations (colon polyps, cancer of other gastrointestinal sites, and desmoid tumors) occur in adults, there are less frequent, sometimes lethal, childhood

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tumors as well, including medulloblastoma, hepatoblastoma, and adrenal cortical carcinoma (13-15). While it is not possible now to prevent those cancers, early detection seems likely to provide the best opportunity for cure (although this hypothesis must be confirmed). As we learn the phenotypic range of these newly identified cancer-predisposing genes in families not selected for linkage analysis, it seems relevant to include children in the research studies. Finding increased risk of cancer or other diseases in children would provide medical justification for testing them.

(b) It is well known that cancer is a multistage process, even in individuals with a genetic predisposition for it. Thus, the biology of carcinogenesis may need to be a major consideration in the development of prevention and intervention programs. Prevention strategies might be applied long before the cancer occurs. For example, for breast cancer, the time to initiate prevention may be at an early stage in breast development (16), before puberty or before breast tissue begins to proliferate. While no clinical trials testing such hypotheses are presently ongoing or proposed, it seems likely that programs in prevention will have to focus to some degree on childhood.

(c) In addition to the biological factors that affect the optimal time for intervention for adult-onset cancers, there are also psychological factors that influence the optimum time for testing, counseling, and intervention. While few data are available on these issues, there has been some concern that adolescence is a time of great focus on body image and might therefore be the worst time to introduce any threat to body image. Wertz et al. (3) have presented data suggesting that revealing information about cancer, serious illness, or adoption to young children helps them cope better with these situations, but there are no data on how people of various ages cope with knowledge of genetic disease or the results of genetic testing.

Given these considerations, we decided that, while genetic testing is not widely available and is being conducted primarily under research protocols (17), the most important recommendations we could make would be to identify areas in which data regarding genetic testing of children are needed so that the data could begin to be collected before genetic testing of children is considered medically indicated or is routinely available on demand.

Understanding Family Response to Uncertainty

It was the consensus within our group that there is an empirical void of data in these areas and that well-defined protocol research should be initiated. The rationale for genetic testing of children in situations for which there is not a specific medical indication has been to relieve uncertainty. However, it was pointed out that we have little data on how families, including children, deal with uncertainty regarding risk of a specific disease in the family. Knowledge of how families cope with that uncertainty in the absence of genetic testing should be determined before introducing the opportunity for genetic testing. Knowledge of prior coping mechanisms then may be incorporated into assessment of the impact of genetic testing and the extent to which testing as compared with other methods may reduce the distress associated with uncertainty. It was suggested

that cognitive and emotionally based psychological counseling for resolving uncertainty-based stress may be one mechanism to reduce stress, while application of DNA testing offers another.

When the basic issues of management of uncertainty are better defined, we can determine the impact of genetic testing of children and the factors that influence it. These factors probably include the patient and family's social, emotional, and economic resources; the way in which the testing is conducted; the child's exposure to or perception of the burden of the disease; and the age at exposure and at testing. It has been suggested that much new information could be obtained by enrolling families with children who have already been tested into a new controlled study of the consequences of testing (18). While those families would be definitely self-selected and not necessarily representative of the general population, future genetic testing may involve largely self-selected families as well. Furthermore, studying families who have already undergone genetic testing may provide significant new data about the need for long-term follow-up.

Family-Based Health Care Delivery

There has been much consideration of the appropriate age for genetic testing of children (2-4,17,18). While most often it has been determined by the medical indication for testing or the ability of the child to provide informed consent, other issues must be considered if genetic testing becomes available on request of the parent. If young children are tested, whether because of medical indication or parental request (e.g., retinoblastoma, in which the average age of onset of the hereditary form is <18 months, necessitates testing of infants), the test results will be communicated to the parents. At present, there is no system to ensure that young patients will be appropriately counseled when they reach the age to decide whether they want to be informed. While there have been no systematic studies about communication of genetic information by parents, at this meeting there were many anecdotes about information that was miscommunicated or not communicated at all. Programs with long-term follow-up and assurance of appropriate counseling must be developed if young children are to be tested.

The need for family follow-up raises the larger issue of the need for a health care system that includes general family counseling. While individual autonomy must not be sacrificed, in many instances multigenerational counseling may be appropriate. The health experience and testing of one generation may have a major impact on decision making in another, and no one has reported monitoring that impact and assessing the different needs of different generations under different conditions. Examples of cases in which this might be appropriate were presented at this meeting, including the case of an individual found to have colon cancer and to be a carrier of one of the HNPCC genes at age 45 years, who might have a child in his or her twenties who is considering reproductive choices or has already conceived. Thus, a diagnosis in one generation may have a dramatic effect on others and necessitates counseling that addresses the concerns of each generation.

Continuing the theme of multigenerational counseling and the need to consider family dynamics with respect to evaluating

genetic testing in children, it was suggested at this meeting that there may have been too much emphasis on the child independent of the parents and that, for some issues, it might be more effective to focus on the family as a unit. For instance, family assessment might be appropriate for determining readiness for testing, monitoring, coping with uncertainty, and evaluating the consequences of testing. It was thought that there was a need to determine whether it is in the child's best interest to meet the parents' needs to deal with certainty or uncertainty, as the parents' ability to cope might have a large effect on the child. These many variables must be evaluated by research teams that include child psychiatrists and developmental psychologists, in addition to behavioral scientists, psychologists, psychiatrists, medical geneticists, pediatricians, and family physicians.

Summary Recommendations

This discussion group recommends that this window of opportunity before genetic testing is available on a widespread basis be used to do the following:

1) Determine how families deal with uncertainty regarding their genetic disease in the absence of genetic testing.

2) Assess the impact of genetic testing (and the impact of the failure to offer genetic testing) on children and how it is affected by age, type, and amount of counseling and follow-up, patient and family resources, and perception of disease burden. Some of these data could be obtained from families already involved in genetic testing.

3) Evaluate the needs of families as units to prepare for testing and the impact of testing and counseling, as contrasted with the needs of the child alone, e.g., the benefit to the child from meeting the parents' needs for genetic testing.

4) Develop model systems of health care delivery that include the child as well as adult psychologists or psychiatrists, multi-generational counseling, and long-term follow-up to evaluate the consequences of counseling and to ensure that, when children who are tested are too young to be informed of test results, they will be educated about their test results at the appropriate age.

5) Continue basic research on the clinical implications of the effects of cancer-predisposing genes in childhood and the optimal time for prevention and intervention.

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Testing and Counseling Adults for Heritable Cancer Risk

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A summary of recommendations from a breakout session of a Workshop on Hereditary Breast, Ovarian and Colon Cancer held in Washington, DC, in April 1994 is presented here. The focus of the session was the provision of testing and counseling services for adults at increased risk for developing cancer. Elements of service provision involving three time-points for counseling (pretest education, risk notification, and follow-up) and suggested areas of research are outlined for discussion. [Monogr Natl Cancer Inst 17:115-118, 1995]

The major contribution of family history to the risk of developing breast and colon cancers has been appreciated for decades. Recently, genes responsible for familial adenomatous polyposis (FAP), Li-Fraumeni syndrome, hereditary nonpolyposis colon cancer, and breast and ovarian cancers have been identified (1-11). While the vast majority of cancers remain the result of complex interactions between genes and the environment, susceptibility to certain familial cancers are inherited. These cancers present scientific as well as ethical and practical challenges to geneticists and oncologists caring for individuals from families affected by inherited cancers. This article summarizes a discussion in a breakout session addressing research and service needs in cancer-risk counseling for adults.

The breakout session focused on essential components of hereditary cancer-risk counseling for adults who face choices about genetic testing. Issues to be considered in establishing counseling services were enumerated; however, it was felt to be premature to suggest specific guidelines for practice. There was consensus among participants that research remains essential to determine necessary components to both the process and content of cancer-risk counseling for adults who may undergo genetic testing. Six recommendations were formulated for consideration by professional societies and policymakers to influence the evolution of testing and counseling services for adults considering testing for heritable cancer predisposition. These arose from discussion by a self-selected collection of physicians, nurses, genetic counselors, and other interested health-care professionals, and need to be considered and debated by additional interested groups, including consumers of such services.

Workshop participants declined to delineate either the appropriate populations to whom genetic testing should be offered or the specific types of health-care professionals that should be involved in the testing and counseling process. Rather, education and counseling issues for a variety of health-care professionals and consumers were described.

Recommendations

Testing and counseling for heritable cancer risk have occurred only in academic research environments. The experiences of participating researchers and publications of others contributed to the recommendation that all aspects of such counseling services be formally evaluated to provide data regarding their effectiveness and impact (12-14). The most essential and least desirable elements of predisposition testing programs have not yet been defined. Eventually, testing and counseling services will undoubtedly be offered in the primary care arena, and research data will help to develop efficient and effective counseling that may be exported to that setting.

The recommendations from the session included:

1) *That efforts be extended to educate the public in the basic concepts of genetics, including risk and probability, and the specific concept of cancer susceptibility.*

There is growing recognition that genetic literacy is essential to decision making about testing (15,16). A more educated public will be better prepared to make informed decisions about testing by appreciating the limitations of genetic information for cancer risk and understanding its potential uses and abuses. This will help to ensure that informed consumers appreciate the importance of voluntary, autonomous testing. Predictive testing is not useful or desirable to all at-risk individuals. More educated consumers will be less likely to undergo testing solely in response to persuasive advertising or because of a misperception of its potential impact (17).

Science illiteracy is rampant (18-21). Furthermore, there is common misunderstanding of the meaning of numbers, particularly risk factors. Even studies of mathematically sophisticated individuals have demonstrated a lack of rational interpretation of risks (22). People judge risks based on their perceived burden (23). In the cancer genetics testing arena, it will undoubtedly be challenging to teach people the uncertainty of reduced penetrance and the abstract concept of susceptibility (24).

2) *That policymakers and administrators be encouraged to include genetic services, specifically predisposition testing and counseling, as health-care delivery is redesigned nationally.*

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Access to care in the provision of heritable cancer-risk testing and counseling services remains a critical concern, given the current inequities in the overall delivery of genetic counseling services. Patients should have access to a multidisciplinary team to provide the education, counseling, and medical management aspects of their care. It is essential that all members of society have access not only to testing and counseling, but also to the medical resources necessary for them to manage their risks, even if expensive surveillance or therapeutic procedures are proposed and chosen.

3) *That health-care professionals currently active in genetics, medical and surgical oncology, and the primary care disciplines all require further training to be prepared to provide appropriate genetics testing information and counseling regarding cancer risk.*

Many health-care providers are not yet even aware of their need to know about predisposition testing for hereditary cancer (25). While some progress has been made in increasing physicians' knowledge of genetics and genetic testing, particularly in specialties that involve tests (e.g., pediatrics and obstetrics), insufficient progress has been made to prepare physicians-in-training for the increasing requirements for genetic testing, education, and counseling projected in oncology (26). More work is needed to determine effective ways for medical and nursing education to incorporate a genetic point of view throughout their curricula. Efforts in continuing medical and nursing education are also needed (27).

Practice guidelines should eventually be developed for genetic testing and cancer-risk counseling through a mechanism, such as a National Institutes of Health (NIH) consensus conference. For example, guidelines for predictive testing for Huntington's disease and Li-Fraumeni syndrome have helped to establish standards of practice (14,28). Both were developed with input from many consumers and medical providers to best serve at-risk individuals.

4) *That consumers be involved in the evolution and evaluation of testing and counseling programs.*

Consumer involvement in the formulation, distribution, and execution of guidelines for testing for Huntington's disease as well as testing for p53 and other disease genes has been critical (28,29). Consumers' contributions to experiences in the development of education and decision-making tools may result in a more balanced presentation of issues facing members of high-risk families. The National Breast Cancer Coalition has released a statement cautioning against the premature use of genetic testing for predisposition to breast cancer, enlightening its constituency about remaining unanswered questions (30).

Moreover, consumers in the breakout session recommended that a system of peer support be promoted for members of families with hereditary cancer. Currently, there are support groups for Li-Fraumeni syndrome (Dana-Farber Cancer Institute), Von Hippel-Lindau disease (VHL Family Alliance), and familial adenomatous polyposis (Johns Hopkins University). These groups are evidence of the ongoing needs of individuals from families at high risk of cancer, even prior to the availability of genetic testing. The Alliance of Genetic Support Groups has received an increasing number of inquiries from members of families with hereditary breast, ovarian, and colon

cancers (Weiss J: personal communication). Thus, it is reasonable to assume that an increasing number of such support groups will be established in the near future. Since consumers will undoubtedly be involved in follow-up support, it is important that they understand and have a role in the development of the services.

5) *That there be standards developed for the performance of DNA testing for cancer susceptibility.*

The vast majority of cancer DNA analysis has been done in research laboratories on a small scale and results offered to patients as a clinical application of these research endeavors. Standards need to be developed and implemented in an expeditious manner because of the intense clinical and commercial pressures to initiate such testing. These standards will be challenging to design and to implement, since the transition of a test from the research laboratory to the clinical setting is complex (31).

Standards must address not only test accuracy and the execution of laboratory testing, but also test interpretation. Regulatory bodies that have been charged with test regulation (Food and Drug Administration, Health Care Financing Administration, and others) will need to be involved in this process. Laboratories that provide test results to consumers need to be CLIA-certified to be in compliance with current federal law.

6) *That those involved in the development of testing and counseling programs consider the following:*

(a) The critical importance of fully informed consent (including social and psychologic risks and benefits) and autonomous decision making in genetic testing. This may be best assured by providing susceptibility testing within the context of genetic counseling.

(b) The possibility of disease (gene or cancer)-specific protocols. The wide variation in organs at risk, age of onset, and cancer-risk management options associated with different predisposing genes makes it likely that testing and counseling programs will not be uniform.

(c) The essential inclusion of nongenetic risk factors in discussions of genetic cancer-risk assessment. Little is known about interactions of environmental, reproductive, and other risk factors with genetic susceptibility. However, individuals found not to have mutations in susceptibility genes should not be reassured that they will not develop cancer.

(d) The desirability of pre-entry physical examination to identify cancer if already present. Predictive testing should not be confused with diagnostic testing. Cancer gene testing is not cancer detection. The psychologic issues for someone undergoing testing to learn whether they may develop cancer in the future differ significantly from the issues for those undergoing evaluation to detect the presence of cancer. There is precedent for this suggestion in the Huntington's disease predictive testing guidelines that include thorough neurologic examination prior to testing (28).

(e) The recognition of the potentially powerful psychosocial and emotional impact of participation in predisposition testing and counseling programs. It is important for preliminary psychologic assessment both to tailor appropriate education and counseling strategies and to provide the opportunity for evaluation of signs for postponement (or, rarely, exclusion) from test-

ing. This is not intended to advocate paternalism, but rather to promote the importance of psychologic assessment in encouraging patients to fully consider their circumstances, particularly at difficult times in their lives. Rarely, individuals may demonstrate sufficient emotional fragility that formal clinical psychologic evaluation may be advisable prior to disclosing results. Indications for postponement include clinical depression or severe anxiety. Use of psychologic assessment tools also furthers the opportunity to collect valuable research data on the emotional impact of testing.

(f) The need for coordination of care and information for members of families who may not reside in a single location and would like to participate in testing and counseling in their own communities.

Elements of Testing and Counseling Programs

In discussing the development of testing and counseling programs, the session participants developed a list that was not intended to be comprehensive but rather attempts to outline some essential elements. Programs involving three visits were envisioned: pretest education and counseling, risk-notification counseling, and follow-up counseling. Research is under way and more is needed to determine the optimal and minimal number of visits that are effective and/or necessary to accomplish autonomous supported decision making with outcomes perceived to be favorable by those who choose to participate.

Aspects of Pretest Education and Counseling

- Comprehensive informed consent (written and verbal)
- Discussion of risks to insurability
- Exploration of potential breaches of confidentiality
- Limitations of information (test results, penetrance, options)
- Summary of medical surveillance and prevention options
- Evaluation of motivations and expectations over time
- Exploration of financial concerns for counseling and medical interventions
- Assessment of coercion to undergo testing by family members or health-care professionals

Aspects of Risk Notification

- Encouragement participation of companion/support person
- Review of limitations of the information
- Identification of second thoughts or misgivings
- Preservation of privacy
- Provision of test results
- Crisis support
- Medical management options

Follow-up Counseling

- Ongoing access by telephone for questions/concerns
- Continuity in providers
- Access to ongoing support resources
- Assurance of protected confidentiality
- DNA banking issues
- Fulfillment of an obligation to recontact when new information becomes available
- Ongoing availability of psychologic counseling
- Introduction to peer support organizations

Research Agenda

It was agreed that important aspects of inherited cancer predisposition testing and counseling have not been adequately evaluated. A research agenda was suggested that reinforced the

importance of the questions raised in the request for application (RFA) HG-94-01 funded by the National Center for Human Genome Research/National Cancer Institute/National Institute of Mental Health/National Institute of Nursing Research at NIH. The overall goal of this RFA is to identify clinical practices that best increase individual and provider understanding of genetic testing for cancer susceptibility. Objectives include identifying the meaning and implications of test results, as well as strategies to promote health, to prevent the development of cancer, and to reduce the risk for test-related psychologic harm, stigmatization, and discrimination in individuals tested and their family members. Furthermore, the need for the development of diverse models for patient education, the exploration of knowledge assessment tools to ensure informed consent, the determination of desired information and manner of presentation, and the examination of modifications for culturally sensitive programs was acknowledged by participants in the breakout session.

Conclusion

Many issues will require careful consideration as new programs to provide adults with genetic testing and counseling regarding heritable cancer risks evolve. It behooves professionals involved in these services to participate in efforts to address the research questions.

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Patient–Provider Relationship in the Context of Genetic Testing for Hereditary Cancers

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Scientific research into the hereditary factors associated with the detection, prevention, treatment, control, and cure of cancers of the breast, ovary, and colon is proceeding at an astonishing rate. The body of knowledge produced by these efforts is expansive and promising, generating new hopes for the eradication of disease and the improvement of human health. As molecular and genetic scientists continue to advance knowledge of cancer-predisposing mutations, the public health impact of their discoveries is beginning to unfold.

Recently, tremendous advances in the field of breast cancer have prepared the way for unprecedented opportunities to detect and forestall devastating disease in women who are at risk for developing breast cancer. A woman with the inherited BRCA1 defect faces an approximately 85% risk of developing breast cancer by the age of 70. Clearly, as genetic testing for breast cancer susceptibility and other cancerous conditions reaches the marketplace, these opportunities will invite both admiration and ambiguity. On the one hand, recent advances in scientific knowledge of hereditary cancers exemplify progress and power. On the other hand, there is considerable uncertainty regarding how this knowledge should be applied and who should have stewardship over its products and effects. As knowledge of the genetic features of these cancers continues to grow, new questions emerge regarding the appropriate way to disseminate this knowledge beyond the research community and into the public and professional domains.

The specific question highlighted in the following article considers the issues in genetic testing for heritable cancers believed to be important to the patient–provider relationship. The discussion group attempted to explore these issues from an ethical perspective and focused on the degree to which the ability to test for cancer-predisposing genetic mutations may alter the nature of the patient–provider relationship and any of the ethical obligations inherent in it.

Patient–Provider Relationship

Working group participants represented a diverse set of interests, including the scientific, clinical, psychological, ethical, and consumer perspectives. Although individual participants emphasized particular issues germane to their fields, a consensus was achieved by the group that many of the emergent issues regarding genetic testing raised concerns about the ethical responsibilities of providers to counsel, educate, treat, and advise patients about individual and family genetic risk. Most discussants agreed that decisions regarding the advisability of genetic testing for heritable risk are a subset of those decisions that characterize the patient–provider relationship.

Historically, the relationship between a doctor and a patient has been considered to have a special integrity and value of its own. In the Middle Ages and later centuries, the oath of Hippocrates embodied the highest aspirations of the physician. It stated that the physician was ethically obliged to do what is in the patient's best interests, to refrain from doing any harm, and to keep confidential all information about the patient (1). Although contemporary models of the relationships between patients and health care providers often eschew the paternalism embedded in this tradition and place greater emphasis on patient autonomy (2), the ethical ideals of beneficence, confidentiality, trust, and non-maleficence it advocated continue to play a significant role in ethical decision-making.

Although members of the working group recognized the fundamental importance of these basic ethical principles to the integrity of the patient–provider relationship in the context of genetic testing, two other issues received more sustained discussion. These issues were 1) the prevailing uncertainty regarding the proper way to educate providers so that patients could make responsible and informed decisions regarding the risks and benefits of testing as well as the consequences for self and family with regard to test results and 2) the need to improve communications with patients, providers, and the public in order to promote a climate of trust and accountability in both the research and practice settings.

Roles and Responsibilities of Patients and Providers

The rapid acceleration of genetic technologies from the research milieu to the clinical area raises an important question regarding who is (or becomes) the *patient*. Traditionally, doctors have been bound by the ethical obligation to use medical knowledge for the benefit of the individual patient or to promote in the patient a sense of well-being. The ability to test genetically for cancer susceptibility in an individual patient provides knowledge that, by implication, directly affects the lives of individuals other than the specific patient seeking information or care. To whom does the genetics professional owe his or her primary allegiance? Is it to the individual patient, who has come to expect that individual rights to autonomy, beneficence, privacy, fairness, and trustworthiness will be honored? Can

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these rights and responsibilities be extended meaningfully to the family unit without compromising their ethical substance? Or is the genetics professional primarily responsible to society, to persons not yet or never to be born because of their risk factors for disease? These questions are not purely rhetorical; they relate directly to our educational efforts and how to target them for the public as well as the professionals. On a larger scale, they require consideration of whose values direct the process of knowledge dissemination and education regarding fundamental health matters that have both private and public implications. They suggest the need for caution and serious debate regarding the kinds of policies and standards necessary to ensure appropriate protection of individual rights and liberties, while concurrently promoting preventive medicine and public health initiatives.

Another emergent issue concerns the question of who is (or becomes) the *provider*. Is it the geneticist, the laboratory, the counselor, the oncologist, or the primary health care professional? Is the provider operating within a therapeutic relationship with the patient, or is the relationship a commercial one, where commodities are exchanged and responsibilities diminished? What additional training in genetics will be necessary to ensure that health care professionals providing genetic testing, education, and counseling services provide them in ways that are sensitive to an individual's level of understanding and need, with special attention to issues of culture, race, ethnicity, sex, personal learning factors, psychological strengths, and value preferences?

Clearly, the responsibility of the provider of genetic testing continues to include the traditional ethical obligations of respecting patient choice through the provision of information regarding risks, benefits, harms, and burdens associated with proposed therapeutic interventions. Yet it will also require discussion of the consequences of obtaining genetic information to one's self and/or family, as well as disclosure of the *uncertainties* that currently limit the scope of this knowledge.

Most discussants acknowledged that the diversity of contemporary settings for the delivery of health care creates a similar diversity in the type of patient-provider relationship. It was also noted that reforms in health care planning and delivery as well as economic restructuring will produce changes in the roles and responsibilities of patients and providers. Many of these changes may further complicate the perceived problems associated with the availability and use of genetic testing for heritable cancer risk.

Access to Genetic Testing

To date, no reliable consensus has been formed regarding how scientific and professional communities should respond to the public's intense pressure to have access to "the test." Recent nationwide surveys indicate that 80% of the American public expects genetic technology to be beneficial, 71% believe it would pose risks to them or to their family, and as many as 62% indicated they believed the benefits would outweigh the risks (3).

Empirical studies by Lerman et al. (4) indicate that, among women with a family history of breast or ovarian cancer, 75% of

first-degree relatives of women with ovarian cancer indicated that they definitely would want to be tested for cancer susceptibility, while 20% indicated they probably would. One of the questions raised by these data is whether genetic testing should be made accessible and affordable to all those who desire it or whether it should be restricted to those individuals who fall in high-risk categories. These decisions will likely become more complex as managed care and competition structures have an impact on the availability and accessibility of health care resources.

In addition to the uncertainty surrounding the issue of who should have access to genetic testing for cancer risk, there is ambiguity associated with the "meaning" of genetic testing. A survey of relevant legislation pertaining to genetic services suggests disagreement on how the terms "genetic testing" and "hereditary" should be defined; this survey demonstrates a wide diversity in the scope of laws relating to confidentiality, informed consent, privacy, discrimination in insurance and employability, and other concerns related to genetic testing (5). Some research demonstrates that, in addition to cost, perceived severity of the disease, and information provided about risks and benefits of genetic testing, the way a testing option is presented to patients may influence public interest in it (6). This finding raises important normative issues regarding patient trust and power and the possibility of provider bias in regard to issues of access and equity. These issues are made more complex by a society that is deeply divided regarding the proper role of government intervention in private lives, the role of personal responsibility in health matters, and the clash between individual liberties and public rights.

Communication About Genetic Risk

Lerman and Schwartz (7) have found that many women, despite their increased risk for developing cancer, do not adhere to recommended breast cancer-screening guidelines. This finding has an important ethical dimension, for it raises questions regarding how "patient benefit" is to be defined and by whom and whether disclosure of test results causes more harm than good. The harms may not be limited to psychological ones, but could include legal, social, and moral harms as well. More research is needed to help clarify what constitutes a "burden" to individual patients and whether knowledge of one's genetic predisposition to breast or ovarian cancer produces in individuals or families a sense of anxiety, stigma, guilt, shame, or genetic discrimination.

To study the motivations of women at high risk for cancer susceptibility and who want genetic testing for BRCA1, Lerman et al. (4) have documented the following: desire to learn about risk to one's offspring, childbearing concerns, reassurance, and need to obtain screening information that might affect an individual's personal health care decisions. This finding of diverse motivations in seeking genetic testing for cancer susceptibility suggests that traditional carrier status counseling, which focuses primarily on the risk to one's offspring, will not be sufficient. Moreover, the authors suggest that women at high risk who seek genetic testing also demonstrate higher levels of psychological distress regarding risk notification, thus raising concerns about psychological vulnerability and its impact on the

informed consent and/or counseling process as well as physician obligations to maximize patient benefit, to minimize harm, and to promote patient trust.

Increasingly, some believe that family physicians and other primary care practitioners will be intermediaries between genetic technology and the individual patient and will be expected to critically appraise the appropriate application and limitations of genetic tests to individual patients (8). This has astounding implications for practitioners as well as for medical school curricula and raises concerns about professional competency to interpret lifetime risk assessments for cancer susceptibility and the need to make appropriate judgments regarding genetic counseling of women and/or their relatives (9). Thus, although the clinician's imperative to keep abreast of medical knowledge and the current standards of care has always been important, the sheer breadth of knowledge in genetic science during the past several years makes this an enormous challenge. The manner in which these challenges are faced will determine the nature of scientific accountability and public trust.

A consensus seems to have been formed that more qualitative research is necessary regarding patterns of knowledge dissemination and styles of communication regarding genetic testing; application of research findings to the clinical area should be based on standards of evidence acceptable to the scientific communities and adapted to accommodate patient, provider, and public values. For some time, health care professionals, bioethicists, and policy analysts have held that the mere availability of a test or technology is not in itself a sufficient criterion for its routine implementation. Groups such as the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, The Hastings Center, and the National Academy of Sciences have articulated several desirable criteria for the clinical application of these technologies: 1) Goals of the testing program should be well defined and attainable; 2) tests should meet standards of reliability and accuracy; 3) provisions should be made for patient education, informed consent, and counseling; 4) a mechanism for quality control should be in place; 5) costs should be acceptable; and 6) there should be adequate follow-up services (6).

Recommendations

Participants in this working group all agreed that the social, psychological, ethical, and professional issues associated with genetic testing for heritable cancer risk are critically important and that further research into these areas is necessary. Investigations of the quality of patient-provider communication are needed so that information is provided in ways that would facilitate competent disclosures by health care providers of the "meaning" of genetic tests, including areas where the predictive value of the test may be uncertain or may have a negative impact on members of the patient's family. In addition to needing competent explanations of basic genetics, patients will need information about potential benefits and risks associated with knowing one's susceptibility status, the limitations of this knowledge, and the rationale for recommendations regarding surveillance, prevention and treatment options, and follow-up. Although standards of care for genetic counselors have in the

past focused on nondirective counseling, genetic counseling for cancer susceptibility may challenge this norm and may indicate the need for alternative methods of counseling. At a minimum, an ethically valid counseling process for heritable cancers would need to include personal risk modification for each woman; awareness and understanding of the individual's comprehension and adjustment to the information provided; competent advice on available options for prevention, treatment, and/or clinical management; and adequate disclosure of provider bias (if any) regarding the degree to which counseling efforts favor nondirective or provider-directed perspectives. Finally, since the ethical justification for any treatment or procedure is determined by the degree of benefit to the individual patient that can be derived from it, it seems prudent to be cautious about genetic testing in areas where this benefit has not yet been established.

Discussion

The availability of genetic testing and other technologies to detect cancer susceptibility provides an important opportunity to re-examine the nature of the patient-provider relationship and to clarify the scope of the ethical responsibilities inherent in it. Many have noted that the genetic revolution poses enormous challenges not only to the scientific and medical communities, but also to the public (10). These challenges are made more complex by health care reform efforts, generalist physician and primary care initiatives, managed care arrangements, and fiscal scarcity. The lack of effective guidelines for the communication of genetic information about breast cancer susceptibility or for providing recommendations and follow-up care for those discovered to carry the gene is a serious problem now confronting providers, patients, and the public. Given the rapidly increasing availability of genetic diagnostic services and the range of related issues noted above, the consensus of the workshop is that further research is necessary to establish the evidentiary standards necessary to generate state and federal policy that is rationally sound, ethically justified, and scientifically based.

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Advocate Participation in the Context of Genetic Testing for Hereditary Cancers

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Research into genetic markers for hereditary cancers is proceeding at an astonishing rate. Although essential to scientific progress, the discovery of the association between genetic features and the consequent development of cancers in humans raises as many questions as it answers. The questions become increasingly complex as the scientific knowledge of hereditary factors in cancer continues to expand and the ability to detect or prevent such cancers becomes a reality. For example: What is the relevance of personal, public, and social consequences related to medical research and technologies? What involvement could—or should—the beneficiaries of predictive genetic testing contribute to research design, evaluation, oversight, data monitoring, and acceleration of viable concepts from “the bench to the bedside”? What responsibility should a patient be permitted—or the clinician relinquish—in making decisions about the “best” treatment for the individual? How reasonable is it to suggest that the patient and clinician share responsibility for ensuring, and invest the time to ensure, that both have the information necessary to make an informed decision about the medical management of disease? Does the concept that the health-care provider and health-care consumer share compatible goals and expectations translate into practical application? What right—or responsibility—do the policymakers, scientists, clinicians, and patients have to balance the resources available to address the needs of society, while remaining sensitive to the needs and interests of the individual?

The balance between individual interests and societal good becomes a confusing, and sometimes impassioned, issue. Professionals articulate compelling arguments on behalf of the population their science is designed to investigate or treat. Can they fully appreciate the interests, desires, concerns, and priorities of the individuals they presume to represent?

The perspective of the “beneficiary” of scientific progress must be included as a vital component of the decision-making process on oversight committees, monitoring panels, and in study sections. Traditionally, this function has been performed by well-trained professionals and monitored by Institutional Review Boards (IRBs). It is now recognized, however, that the perspective of the beneficiary of these decisions has been sorely missing from the process. It is here that the advocate can serve a critical function.

By definition, an advocate is “one who pleads another’s cause.” In the context of genetic testing, the advocate functions to ensure that the rights and interests of individuals who are subjects of genetic testing are supported, protected, and defended. The information obtained from genetic testing may lead to both beneficial and burdensome consequences. Therefore, it is imperative that those providing or interpreting the test or disseminating

the results perform their duties responsibly and appropriately.

Advocates suggest that the complex issues facing genetic researchers and clinicians related to breast cancer could be reconciled through a collaborative effort between scientists and advocates. Determining what is “responsible” when conducting genetic testing and ways that are “appropriate” for disseminating results can be achieved best with the added perspective of the advocate. In addition to helping to establish protocols for genetic testing and dissemination of test results, advocates can assist in promoting a research agenda and complementing the distinct network of scientific, medical, public, and clinical collaborators. Their participation is vital where the needs and rights of individuals are paramount, whether in the development, execution, or evaluation of clinical trials. Advocacy efforts should focus on values that the research process might challenge, including autonomy, self-determination, empowerment, and individual responsibility for one’s health care. Advocate involvement should also include assisting patients/clients in understanding relevant information, ensuring that informed consent is effective, and relaying client values, beliefs, and attitudes that influence participation in clinical trials to the research community. Their influence could—and should—influence how genetic testing is implemented in communities where clients reside.

A common goal among researchers, health-care providers, allied health professionals, consumers and their advocates is the desire for knowledge that will increase understanding about one’s susceptibility to heritable disease(s) and assist in making therapeutic treatment decisions. To this end, advocates must be a liaison between the legitimate rights and needs of clients and the legitimate responsibilities and interests of researchers and providers, extending the role of the IRB. However, in serving as an instrument of the *client’s* needs and interests, advocates cannot make decisions for clients based on personal interests.

The advocate’s sole function is to safeguard the fundamental rights and responsibilities inherent to biomedical and behavioral research. It is reasonable to expect that everyone involved in the process should serve as an advocate, assisting in ensuring that these safeguards are elements of research and testing protocols.

The following recommendations have been synthesized from discussions held at the National Cancer Institute Workshop on Hereditary Breast, Ovarian and Colon Cancer, as well as from the experiences and insights of the author.

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1) Advocate involvement is a critical component when establishing genetic research and testing protocols. The advocate's role must be clearly defined and recognized as vital, not incidental, to the process. Advocacy requires the ability to articulate the myriad of tangible and abstract issues facing potential beneficiaries of genetic susceptibility testing for breast, ovarian, or colon cancer. Advocates should remain committed to clearly defined goals that address the specific needs and desired outcomes of the individual/group they represent.

2) When establishing protocols, it is imperative to acknowledge, and accommodate, the unique reactions of each individual to receiving information about genetic risk, specifically for breast, ovarian, and colon cancers. Caution must be taken to avoid making assumptions on the basis of sociodemographic characteristics. For example, educational level does not determine how genetic information is processed and acted on. Personality and coping styles, one's ability to deal with uncertainty, and ethnic and cultural differences must all be considered as part of the "formula" when determining the benefit or value of such information to the individual. Fortunately, studies are under way to determine the psychologic implications, coping styles, and counseling interventions. Advocates, if involved to the fullest, provide the impetus for consideration of these critical issues.

3) It is vital that the advocate's sphere of concern and influence include issues related to the content, process, and timing of delivery of genetic information, with the single motivating factor being the impact of risk notification on any individual implicated. The goal is to reduce potential harm to participants, not to unduly constrain investigators. Likewise, the advocate can—and should—support funding, recruitment, and training of scientists as well as improved coordination between scientists, helping to communicate the importance of clinical trials to communities, policymakers, funding sources, and potential participants.

4) Predisposition testing for breast, ovarian, and colon cancers cannot be conducted "out of context." Safeguards must be established that protect the individual's right to know—and right not to know—and to provide such information in a manner that is comprehensible to the recipient. The advocate can influence the design of protocols that ensure that those rights are recognized.

5) Advocates can help bridge the gap between the research community and the public, helping to communicate the impor-

tance of clinical trials to the affected community and enabling trials to enroll informed and willing participants. Serving as "activists," advocates can be influential in drawing attention to the issues at local, state, and national levels among consumers, providers, and researchers and can contribute to improved processes and outcomes on behalf of those for whom the advocate "pleads."

As difficult as it may be to satisfy the questions and concerns expressed by advocates, their role must be taken seriously. It is critical to the successful and responsible execution of genetic testing that the issues they raise be resolved. Researchers and clinicians must stand among the ranks of the most vehement of advocates in examining the strategies used to determine genetic risk for disease, to consider the implications of the availability of this information and, more important, to preserve the fundamental rights and interests of the individuals whose lives will be altered by this knowledge. The scientist's/clinician's concern or influence must not be limited to his/her sphere of professional expertise or allow personal communication skills and/or "comfort level" to set the standard for execution.

Genetic test results are—or soon will be—a determining factor in making personal and medical management/treatment decisions. Therefore, it is critical that everyone, regardless of their personal or professional gain, work to ensure that the needs and rights of the individuals being tested are protected. If the outcome of genetic research and testing is to be successful, no one can defer responsibility for setting standards for conducting research and/or disseminating results, nor can anyone be excluded from the process. Everyone is obligated to protect the rights and responsibilities of those implicated by this scientific advancement. The involvement of the advocate in the process will help to ensure that it is achieved.

We—the women and men whose lives are affected by breast, ovarian, and colon cancers—have become an increasingly more sophisticated group. Until recently, we could only ask why our health issues were not being addressed. Now recognized as well informed, articulate, and politically astute, we have become an imposing force to the health care industry. Without compromising the quality of medical science, the scientific community is urged to question and challenge the traditional approach of conducting research and providing medical care and to include advocates in the process.

Correction: Prior Annotation of B. Fisher's Papers Incorrect

Medline, CancerLit, and PDQ erroneously annotated certain articles authored or co-authored by Dr. Bernard Fisher with the phrase "scientific misconduct—data to be reanalyzed." All such annotations have been removed or are being removed. However, the Journal published the incorrect annotation in the reference lists of papers that cited those articles. We apologize for any problems or concerns this may have caused. Readers should disregard the erroneous annotations in the papers named below:

- (1) Arnold A: More on endometrial cancer and tamoxifen [letter]. *J Natl Cancer Inst* 86:1877-1878, 1994
- (2) Brandes LJ, LaBella FS, Warrington RC: Response to letter by Morris SA entitled "Re: Enhanced cancer growth in mice administered daily human-equivalent doses of some H₁-antihistamines: predictive in vitro correlates." *J Natl Cancer Inst* 86:1355-1356, 1994
- (3) Carcangiu ML: Re: Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [letter]. *J Natl Cancer Inst* 86:1251-1252, 1994
- (4) Craighead PS: Postoperative radiotherapy after conservative surgery in patients with early breast cancer [letter]. *J Natl Cancer Inst* 87:317-318, 1995
- (5) Fisher ER, Costantino JP, Fisher B: Response to letter by Arnold A entitled "More on endometrial cancer and tamoxifen." *J Natl Cancer Inst* 86:1878-1879, 1994
- (6) Fisher ER, Fisher B, Wickerham DL, et al: Response to letter by Carcangiu ML entitled "Re: Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14." *J Natl Cancer Inst* 86:1253-1254, 1994
- (7) Gal D, Weiselberg L, Runowicz CD: Re: Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [letter]. *J Natl Cancer Inst* 86:1252-1253, 1994
- (8) Lippman ME: How should we manage breast cancer in the breast, or buddy, can you paradigm? [editorial]. *J Natl Cancer Inst* 87:3-4, 1995
- (9) Nayfield SG, Bongiovanni GC, Alciati MH, et al: Statutory requirements for disclosure of breast cancer treatment alternatives. *J Natl Cancer Inst* 86:1202-1208, 1994
- (10) Taplin SH, Barlow W, Urban N, et al: Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. *J Natl Cancer Inst* 87:417-426, 1995
- (11) Veronesi U, Marubini E, Del Vecchio M, et al: Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 87:19-27, 1995

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** Speakers and Session Chairs

It's Time to Take 5

IT'S EASY TO EAT FIVE
OR MORE SERVINGS
OF FRUITS AND
VEGETABLES A DAY...

Keep a bowl of
fruit on your kitchen
counter or table,
within easy reach.



Drink a glass of
100% fruit juice
after a ball game
or workout.

Pick up pre-cut
vegetables or ready-
to-eat salads at your
supermarket's
produce section or
salad bar.



Add sliced bananas
or peaches to your cereal.

Keep a tangerine, apple or
banana on your desk for a
midday snack. Pick one
up from a sidewalk fruit
vendor or convenience
store on your way to work.



Pour fruit juice
in your ice cube tray
and add toothpicks for
homemade fruit pops.

Add more vegetables
to your dinner tonight.
Try chopped zucchini,
cauliflower, carrots
and green peppers.



Don't hide fruits and
vegetables in your
crisper. Keep them
visible on the top
shelf in your
refrigerator.

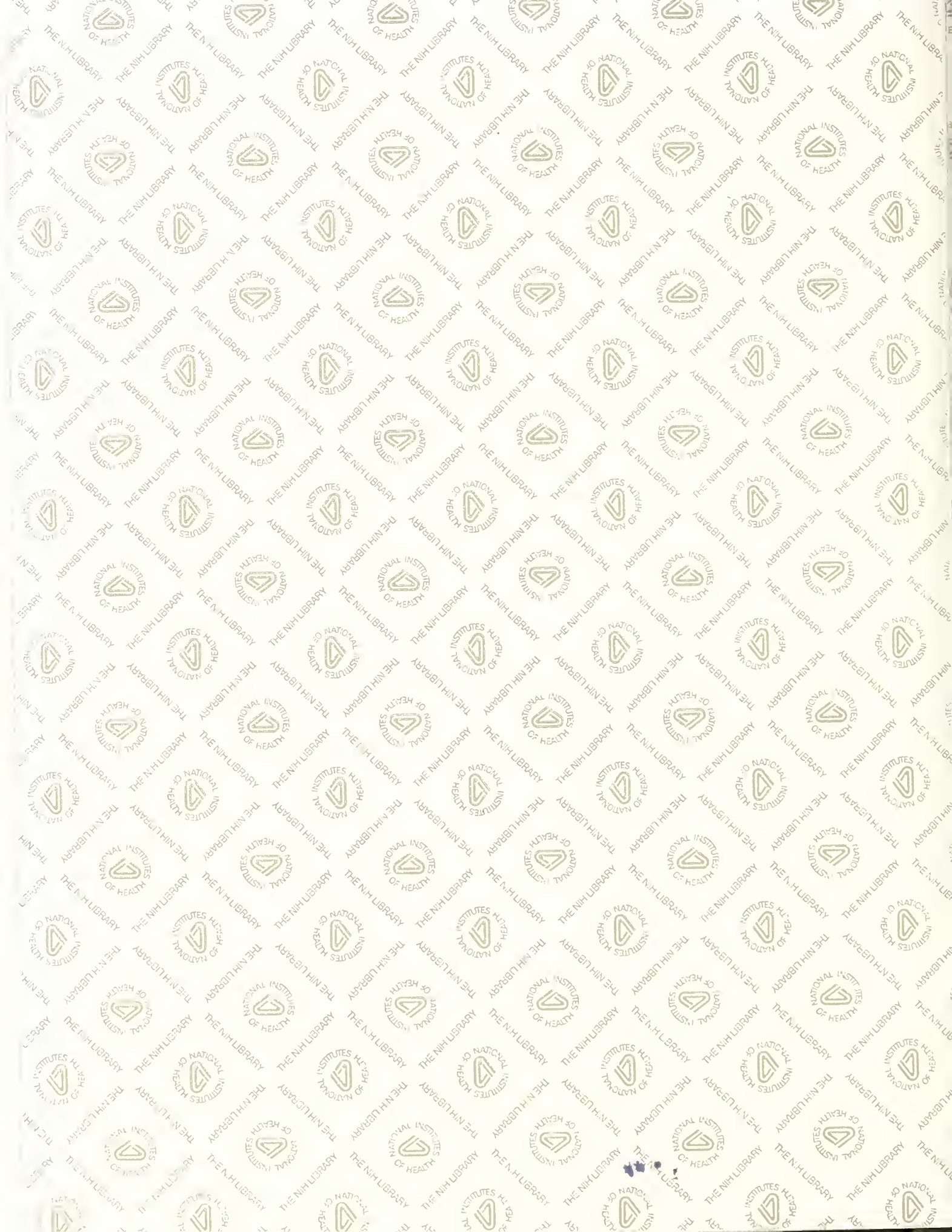
Serve kids a glass
of 100% orange,
grapefruit or
tomato juice for
breakfast.

fruits & vegetables
eat 5 a DAY

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